CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Templates
Version: 2018-01-24

Date:	January 13, 2022
Reviewer:	Benjamin J. Booth, PhD, MS Division of Epidemiology I
Deputy Director:	CAPT. Sukhminder K. Sandhu, PhD, MPH, MS Division of Epidemiology I
Subject:	ARIA Sufficiency Memo for Pregnancy Safety Concerns
Drug Name:	Abrocitinib
Application Type/Number:	NDA 213871
Sponsor:	Pfizer, Inc.
OSE RCM #:	2020-1835

1. BACKGROUND INFORMATION

1.1. Medical Product

Abrocitinib (Cibinqo) is a Janus Kinase (JAK) inhibitor indicated for the treatment of adults with refractory, moderate-to-severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable.[1] Cibinqo is not recommended for use in combination with other JAK inhibitors, biologic immunomodulators, or with other immunosuppressants. Recommended dosage is 100 mg orally once daily; 200 mg orally once daily is recommended for those patients who are not responding to 100 mg once daily; moderate renal impairment: 50 mg once daily; CYP2C19 poor metabolizer: 50 mg once daily or 100 mg once daily for those patients who are not responding to 50 mg once daily.

A boxed warning is in place for abrocitinib labeling that warns of serious bacterial, fungal, viral, and opportunistic infections; higher rate of all-cause mortality; malignancy; major adverse cardiovascular events; and thrombosis.[1] The most common (≥1% of patients) adverse reactions observed in clinical trials were nasopharyngitis, nausea, headache, herpes simplex, increase blood creatinine phosphokinase, dizziness, urinary tract infection, fatigue, acne, vomiting, oropharyngeal pain, hypertension, influenza, gastroenteritis, upper abdominal pain or, abdominal discomfort, herpes zoster, thrombocytopenia, impetigo, and contact dermatitis. The mean elimination half-lives and its two active metabolites, M1 and M2, range 3 to 5 hours.

1.2. Describe the Safety Concern

The Division of Dermatology and Dentistry (DDD) requested that the Division of Epidemiology (DEPI) assess the sufficiency of ARIA for broad-based safety signal detection studies among women exposed to abrocitinib during pregnancy.

Safety during pregnancy due to drug exposure is a concern for women who are pregnant or of childbearing potential. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.[2]

The applicant conducted six studies in the atopic dermatitis clinical development program (n=2,856). As of April 22, 2020, clinical data are available for the use of abrocitinib in seven pregnant women. Five of these women were exposed to 200mg per day: two women had miscarriages and three had unknown outcomes. Two women were exposed to 100mg per day: both had unknown outcomes. Three cases of partner exposure were also identified with all exposed to 100mg per day: one had a full live term birth and two had unknown outcomes.[3]

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[1] Cibinqo label as of January 11, 2022, \\CDSESUB1\evsprod\nda213871\0031\m1\us\lab-1423-0-4-lab-1424-0-4-clean.doc.

[2] Dinatale M. Division of Pediatric and Maternal Health, FDA. The pregnancy and lactation labeling rule (PLLR). https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM520454.pdf. Accessed January 13, 2021.

[3] Applicant's integrated summary of safety, pages 242-243. \\CDSESUB1\evsprod\NDA213871\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\atopic-dermatitis\5353-rep-analys-data-more-one-stud\iss\iss.pdf

Labeling for abrocitinib has the following information regarding pregnancy:[1]

8.1 Pregnancy

Pregnancy Exposure Registry

There (b) (4) a pregnancy exposure registry that monitors pregnancy outcomes in (b) (4) (b) (4) exposed to CIBINQO during pregnancy. Pregnant (b) (4) exposed to CIBINQO and health care providers are encouraged to call 1-877-311-3770.

Risk Summary

Available data from pregnancies reported in clinical trials with CIBINQO are not sufficient to establish a drug-associated risk for major birth defects, miscarriage, or other adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of abrocitinib to pregnant rats and rabbits during organogenesis at exposure 14 or 5 times the maximum recommended human dose (MRHD) based on AUC comparison, respectively, resulted in maternal dystocia and skeletal variations in rats and no adverse effects in rabbits (*see Data*).

The background risks of major birth defects and miscarriage for the indicated population are unknown. All pregnancies carry some risk of birth defects, loss, or other adverse outcomes. The background risks in the U.S. general population of major birth defects and miscarriages are 2-4% and 15-20% of clinically recognized pregnancies, respectively.

Data

Animal Data
In an embryofetal development study, abrocitinib was administered orally to pregnant rats at doses of 10, 30, or 60 mg/kg/day during the period of organogenesis. No fetal malformations were observed. Abrocitinib increased the incidence of skeletal variations of short 13th ribs at 30 mg/kg/day (14 times the MRHD based on AUC comparison). Increased embryofetal lethality and additional skeletal variations (cervical arches with reduced ventral processes, thickened ribs, and unossified metatarsals) were noted at 60 mg/kg/day (22 times the MRHD based on AUC comparison).

In an embryo-fetal development study, abrocitinib was administered orally to pregnant rabbits at doses of 10, 30, or 75 mg/kg/day during the period of organogenesis. No abrocitinib-related maternal or developmental toxicity was noted at doses up to 75 mg/kg/day (5 times the MRHD based on AUC comparison).

In a prenatal and postnatal development study, abrocitinib was administered orally to pregnant rats at doses of 10, 30, and 60 mg/kg/day beginning on gestation day 6 and continuing through lactation day 20. Dystocia with prolonged parturition and reduced offspring body weights were noted at 30 mg/kg/day (14 times the MRHD based on AUC comparison). Postnatal survival was markedly decreased at 60 mg/kg/day (22 times the MRHD based on AUC comparison). No maternal toxicity was observed at 10 mg/kg/day (3 times the MRHD based on AUC comparison). No abrocitinib-related effects on postnatal developmental, neurobehavioral, or reproductive performance of offspring was noted at doses up to 30 mg/kg/day (14 times the MRHD based on

AUC comparison).

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	x

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected

☐ No approved indication, but practitioners may use product off-label in pregnant women

☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized

☒ No approved indication, but use in women of child bearing age is a general concern

2.2. Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty

☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty. †

☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review). †

† ***If checked, please complete General ARIA Sufficiency Template.***

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☒ Pregnancy registry with internal comparison group

☐ Pregnancy registry with external comparison group

☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)

☐ Electronic database study with chart review

☒ Electronic database study without chart review

☒ Other, please specify: Alternative study designs would be considered: e.g., retrospective cohort study using claims or electronic medical record data or a case-control study.

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

☐ Study Population
☐ Exposures
☒ Outcomes
☐ Covariates
☒ Analytical Tools

For any checked boxes above, please describe briefly:

Outcomes: ARIA lacks access to medical records, the prospective registry requires clinical information from medical records and risk factors that may not be available in claims data. The pregnancy registry being considered requires that an expert clinical gynecologist or dysmorphologist review and classify medical records of all major congenital malformations.

Analytical tools: ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been tested for birth defects and other pregnancy outcomes.

2.5. Please include the proposed PMR language in the approval letter.

Two PMRs related to pregnancy outcomes were issued:[4, 5]

(b) (4)

[redacted]

[4] Post Marketing Requirements 4217-4 Pregnancy Registry for Abrocitnib. January 11, 2022. Accessed from \\CDSESUB1\evsprod\nda213871\0031\m1\us\pmr-4217-4-pregnancy-registry.doc.
[5] Post Marketing Requirement 4217-5 Additional Pregnancy Study for Abrocitnib. January 11, 2022. Accessed from \\CDSESUB1\evsprod\nda213871\0031\m1\us\pmr-4217-5-additional-pregnancy-study.doc.

APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BENJAMIN J BOOTH
01/13/2022 10:14:59 AM
Dr. Catherine Callahan was the team lead and provided secondary clearance, but is no longer at FDA.

SUKHMINDER K SANDHU
01/13/2022 10:16:11 AM

JUDITH W ZANDER
01/13/2022 12:31:49 PM

SARAH K DUTCHER
01/13/2022 12:40:45 PM

GERALD J DALPAN on behalf of ROBERT BALL
01/13/2022 12:56:44 PM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology ARIA Sufficiency Memorandum
Version: 2018-01-24

Date:	January 12, 2022
Reviewer:	Joel L. Weissfeld, MD MPH Division of Epidemiology I
Team Leader:	Mingfeng Zhang, MD PhD Division of Epidemiology I
Division Director:	CAPT. Sukhminder K. Sandhu, PhD MPH MS Division of Epidemiology I
Subject:	MACE, Malignancy, and Thrombosis
Drug Name:	abrocitinib (Cibinqo)
Application Type/Number:	NDA 213871
Submission Number:	0002
Applicant/sponsor:	Pfizer
OSE RCM #:	2021-1436

EXECUTIVE SUMMARY *(place "X" in appropriate boxes)*

Memo type	
-Initial	
-Interim	
-Final	X
Source of safety concern	
-Peri-approval	X
-Post-approval	
Is ARIA sufficient to help characterize the safety concerns?	
-Yes	
-No	X
If "No", please identify the area(s) of concern.	
- Surveillance or Study Population	
- Exposure	
- Outcomes of Interest	X
- Covariates of Interest	
- Surveillance Design/Analytic Tools	

1. BACKGROUND INFORMATION

1.1. Medical Product

Abrocitinib is a Janus kinase (JAK) inhibitor seeking FDA approval for treatment of (b) (4) (b) (4) moderate-to-severe atopic dermatitis (AD).

1.2. Describe the Safety Concern

During its review of NDA 213871, DDD used new information about the safety of tofacitinib (another JAK inhibitor) to inform its post-market safety requirements for abrocitinib.[a] As summarized below, the new information substantiated Major Adverse Cardiovascular Events (MACEs), malignancies, and thrombosis as safety risks due to treatment with tofacitinib.[b] Assessing these risks as effects plausibly produced by JAK inhibition in general, DDD categorized MACE, malignancy, and thrombosis as important potential post-market safety risks from abrocitinib treatment for atopic dermatitis.

This ARIA Sufficiency Memorandum presents OSE's ARIA Sufficiency Assessment for abrocitinib and the serious adverse events of MACE, malignancy, and thrombosis in patients (b) (4) (b) (4) with atopic dermatitis.

Four sources of information support concerns about the post-market safety of abrocitinib: (1) randomized post-market study of the safety of another JAK inhibitor, (2) adverse events in clinical studies of abrocitinib, (3) class-wide biochemical toxicities from JAK inhibition, and (4) mechanism of therapeutic action (immunosuppression).

1. Study of another JAK inhibitor (*Phase 3b/4 Randomized Safety Endpoint Study of 2 Doses of a JAK inhibitor in Comparison to a Tumor Necrosis Factor (TNF) Inhibitor in Subjects with Rheumatoid Arthritis*)

   This study randomized ≥50-year-old patients with rheumatoid arthritis and ≥1 cardiovascular-disease risk factor to treatment with (a) a JAK inhibitor 10 mg daily (1456 patients with 3.64-year mean follow-up), (b) a JAK inhibitor 5 mg daily (1455 patients with 3.77-year mean follow-up), or (c) an inhibitor of tumor necrosis factor-alpha (TNF; 1451 patients with 3.77-year mean follow-up). MACE, malignancies, and thrombosis occurred more often in patients treated with a JAK inhibitor than patients treated by TNF inhibition (Table 1).

[a] Pfizer, Final Clinical Study Report (CSR), *Phase 3b/4 Randomized Safety Endpoint Study of 2 Doses of Tofacitinib in Comparison to a Tumor Necrosis Factor (TNF) Inhibitor in Subjects with Rheumatoid Arthritis* (A3921133), June 2, 2021, submitted to NDA 203214 (eCTD 1534) on July 1, 2021.

[b] Integrated Safety Review (ISR), Safety Labeling Changes for Janus Kinase Inhibitors for Inflammatory Conditions (Tofacitinib, Baricitinib, Upadacitinib), filed under NDA 203214 on August 17, 2021 (DARRTS Reference ID: 4842642).

Table 1: Adverse events in treatment groups from the *Phase 3b/4 Randomized Safety Endpoint Study of Two Doses of a JAK inhibitor in Comparison to a Tumor Necrosis Factor (TNF) Inhibitor in Subjects with Rheumatoid Arthritis)*

Comparing treatment with another JAK inhibitor (JAK) 10 mg daily vs. inhibition of tumor necrosis factor-alpha (TNF)				
	Number (%) of patients with event (On-Study)			
Endpoint	**TNF (N=1451)**	**JAK 10 mg (N=1456)**	**RR**	**95% CI**
MACE	43 (3.0)	59 (4.1)	1.37	0.93-2.01
Malignancy except NMSC	42 (2.9)	60 (4.1)	1.42	0.97-2.10
Lymphoma	1 (0.1)	6 (0.4)	5.98	0.72-49.6
Death	38 (2.6)	66 (4.5)	1.73	1.17-2.56
Thrombosis	56 (3.9)	86 (5.9)	1.53	1.10-2.13
Comparing treatment with another JAK inhibitor (JAK) 5 mg daily vs. inhibition of tumor necrosis factor-alpha (TNF)				
	Number (%) of patients with event (On-Study)			
Endpoint	**TNF (N=1451)**	**JAK 5 mg (N=1455)**	**RR**	**95% CI**
MACE	43 (3.0)	50 (3.4)	1.16	0.78-1.74
Malignancy except NMSC	42 (2.9)	62 (4.3)	1.47	1.00-2.16
Lymphoma	1 (0.1)	4 (0.3)	3.99	0.45-35.6
Death	38 (2.6)	49 (3.4)	1.29	0.85-1.95
Thrombosis	56 (3.9)	67 (4.6)	1.19	0.84-1.69

SOURCE: ISR Tables 14 and 16; CSR Table 14.2.2.1; RRs and 95% CIs calculated by DEPI
ABBREVIATIONS: RR – relative risk; CI – confidence interval; MACE – Major Adverse Cardiovascular Event; NMSC – non-melanoma skin cancer

2. Adverse events in clinical studies of abrocitinib

As shown in Table 2, MACE, malignancies, and venous thromboembolic events occurred in NDA study patients during treatment with abrocitinib for atopic dermatitis.

Table 2: Summary of patient demographics, drug exposure, and treatment-emergent adverse events of interest in the Full Cumulative Pool for abrocitinib NDA 213871

Number of patients	3128
Patient age, years, median (IQR)	29 (20-42)
Cumulative drug exposure, patient-years	2089
Number of patients with drug exposure ≥48 weeks	994
Deaths	3

Table 2: Summary of patient demographics, drug exposure, and treatment-emergent adverse events of interest in the Full Cumulative Pool for abrocitinib NDA 213871

Adverse Events of Special Interest, number of patients	
Serious infection	46
Adjudicated opportunistic herpes zoster (HZ)	20
Adjudicated tuberculosis (TB)	0
Adjudicated opportunistic infection excluding TB and HZ	0
Malignancy excluding NMSC	3
Adjudicated Major Adverse Cardiovascular Event (MACE)	4
Adjudicated non-fatal venous thromboembolism (VTE)	6
Other adverse events of interest, number of patients	
Lymphoma	1
Retinal detachment	2

SOURCE: Abrocitinib Safety Update, submitted to NDA 213871, eCTD 0008, on November 23, 2020; Chambers WA, Medical Review by Ophthalmology Consultant, filed under 213871 on January 5, 2021 (DARRTS Reference ID: 4726874).
ABBREVIATIONS: IQR – interquartile range; NMSC – non-melanoma skin cancer
FOOTNOTE: Including events occurring 28 days after treatment discontinuation

3. Class-wide biochemical toxicities from JAK inhibition

Laboratory assessments for NDA 213871 showed relationship between abrocitinib dose and LDL cholesterol (Table 3), a toxicity generally observed from JAK inhibition and a motivating rationale for the cardiovascular outcome trial (Study A3921133) conducted as a post-marketing requirement for tofacitinib (PMR 1934-3).

Table 3: Percent change from baseline at Week 16 in LDL cholesterol for patients with non-missing values at both timepoints (Primary Safety Pool)

Group	N	Δ	SE
Placebo	129	3.8	1.9
ABRO 100 mg	232	9.0	1.4
ABRO 200 mg	232	16.5	1.8

SOURCE: ISS Table PSP.14.3.4.4.2.2
ABBREVIATIONS: LDL – low-density lipoprotein; SE – standard error

4. Mechanism of therapeutic action (immunosuppression)

As immunosuppressives, the JAK inhibitors present similar theoretical risks for opportunistic infection, serious infection, non-Hodgkin lymphoma, and possibly other types of malignancy. Assessments conducted by the Office of Clinical Pharmacology found no

compelling reason to attribute relative safety to JAK inhibitors with different target specificity.[c,d]

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Table 4: FDAAA Purpose

Assess a known serious risk	
Assess signals of serious risk	X
Identify unexpected serious risk	

1.4. Statement of Purpose

DDD characterized the regulatory purpose for a post-market assessment of abrocitinib and the serious adverse events of concern (MACE, malignancies, and thrombosis) as: signal refinement (evaluate the magnitude or clinical significance of a possible association between a drug treatment and a serious adverse event). As indicated by the study description in the following paragraph, OSE assessed sufficiency of ARIA for a study that compares adverse event incidence between atopic dermatitis patients treated with abrocitinib and atopic dermatitis patients not treated with abrocitinib (internal reference group).

Conduct an observational study to assess MACE, malignancy, and venous thromboembolism in patients (b) (4) *with atopic dermatitis during and after treatment with abrocitinib. For each adverse-event outcome separately, compare incidence in the target population against reference rates internally derived from analyses conducted in patients treated with dupilumab or other chronic systemic treatments for moderate-to-severe atopic dermatitis.*

1.5. Effect Size of Interest or Estimated Sample Size Desired

The sample sizes for the desired post-market studies should target estimation of incidence rates for adverse events expected to occur with a frequency of ≈2 to 4 events per 1000 patient-years.[e]

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

For purposes of ARIA assessment, we defined the desired population as patients (b) (4) (b) (4) with atopic dermatitis treated with an agent usually reserved for moderate or severe disease.

Atopic dermatitis is a chronic pruritic inflammatory skin disease that occurs mostly in children, but also in adults. Associated features include personal or family history of atopy (asthma or hay fever) and dermatitis affecting skin creases (antecubital fossae, popliteal fossae, neck, areas around eyes, fronts of ankles). Appropriate modalities for chronic treatment of moderate or severe disease include (1) high- or ultra-high potency topical corticosteroids, (2)

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[c] JAK inhibitors variably target four intracellular enzymes (JAK1, JAK2, JAK3, and TYK2).

[d] ISR, Non-Clinical Considerations, APPENDIX 1, pp 69-82.

[e] Pfizer, Final Study Report: External Controls for Risk Characterization in Support of the Abrocitinib Clinical Trial Program: A Population-Based External Cohort Study using The Kaiser Permanente Northern California Members (B7451044), submitted to NDA 213871 (eCTD 0001) on June 29, 2020, Table 1, pp 23-25.

phototherapy, (3) immunosuppression (with methotrexate, azathioprine, mycophenolic acid, or cyclosporine), and (4) dupilumab.

2.2 Is ARIA sufficient to assess the intended population?

YES. ARIA reliably captures patient age. The Sentinel Distributed Database (SDD) permits identification of patients encountering medical care with a presumptive diagnosis of atopic dermatitis (ICD-10-CM L20). National Drug Classification (NDC) and Current Procedural Terminology (CPT) codes in SDD permit identification of patients with healthcare claims for medical treatments typically considered appropriate for moderate or severe atopic dermatitis. (See Section 3.)

The objectives for the requested post-market evaluation require a real-world sample of patients who receive abrocitinib (or other appropriate medical treatment) for no apparent reason other than atopic dermatitis. ARIA can reasonably satisfy this regulatory requirement, for example, by using diagnosis and procedure codes in SDD to define an exposed cohort of patients with (1) a new (index) pharmacy dispensing for abrocitinib (an inappropriate treatment for mild atopic dermatitis) occurring within 90 days of a previous medical encounter ostensibly for atopic dermatitis (ICD-10-CM L20) and (2) no pre-index medical encounters (within 365 days) ostensibly for any other abrocitinib treatment indication (none currently).

3 EXPOSURES

3.1 Treatment Exposure

For purposes of ARIA assessment, we defined the exposure of interest as treatment with abrocitinib. For certain endpoints (*e.g.*, malignancy), treatment-related events might increase in frequency after a post-initiation latent period or persist after discontinuation of treatment.

3.2 Comparator Exposure

For purposes of ARIA assessment, we considered two reference (comparator) exposures, a broad reference defined by several treatment approaches and a narrow reference defined by one treatment (dupilumab, an interleukin-4 receptor alpha antagonist).

A broad reference might define exposure by any treatment selected from a class (other than JAK inhibitors) typically reserved for moderate or severe atopic dermatitis. Candidate treatment classes include (1) high- or ultra-high potency topical corticosteroids, (2) phototherapy, (3) cyclosporine, and (4) dupilumab. Post-market assessments in SDD might use a broadly defined reference to obtain precise estimates of adverse event incidence in patients with moderate or severe atopic dermatitis. A narrow reference might define exposure by treatment with dupilumab, a modern biologic approved in 2017 for moderate-to-severe atopic dermatitis. (During post-SAM discussions, DDD introduced a requirement for a comparator restricted to "dupilumab or other chronic systemic treatments for moderate-to-severe atopic dermatitis." This definition covers dupilumab and cyclosporine and excludes topical steroids and phototherapy.)

3.3 Is ARIA sufficient to identify the exposures of interest?

YES. NDCs (assigned after NDA approval) will permit identification of patients in SDD with pharmacy dispensings for abrocitinib (an orally administered drug).

NDCs in SDD permit identification of patients with pharmacy dispensings for non-abrocitinib

treatments, including, for example, (1) cyclosporine (*e.g.*, Neoral® oral liquid-filled capsule, NDCs 0078-0246 and 0078-0248) and (2) dupilumab (*i.e.*, Dupixent®, a biologic formulated for self-administration by subcutaneous injection, NDCs 0024-5914, 0024-5915, 0024-5916, and 0024-5918).

ARIA tools generate longitudinal records of outpatient pharmacy dispensings, which permit construction of patient-specific episodes of treatment with abrocitinib or other topical, oral, or self-injectable agents used in patients with moderate or severe atopic dermatitis.

CPTs in SDD also permit identification of medical encounters for phototherapy procedures used to treat moderate or severe atopic dermatitis (Table 4). Individual phototherapy sessions for atopic dermatitis typically occur frequently (*e.g.*, twice weekly) over a period of time defined by clinical response.[f]

Table 4: Current Procedural Terminology for phototherapy and photo-chemotherapy.

CPT	PROCEDURE – LONG DESCRIPTION
96900	ACTINOTHERAPY ULTRAVIOLET LIGHT
96910	PHOTOCHEMOTX TAR&UVB/PETROLATUM/UVB
96912	PHOTOCHEMOTX PSORALENS&ULTRAVIOLET PUVA
96913	PHOTOCHEMOTHERAPY DERMATOSES 4-8 HRS SUPERVISION

DDD presented abrocitinib as a long-term treatment for a chronic condition. As of April 22, 2020 (data cutoff date), 994 (31.8%) of 3128 patients in the Full Cumulative Pool had continued abrocitinib treatment for at least 48 weeks.[g] Therefore, ARIA might reasonably use an intention-to-treat risk window, defined as the 3-year period after an index exposure to abrocitinib (or reference treatment), with follow-up terminating on death, disenrollment, end of study period, Sentinel Data Partner data cutoff date, or (depending on the safety outcome) discontinuation of the cohort-defining treatment.

Abrocitinib and dupilumab present distinct differences for prescribers and patients.

- Abrocitinib is a tablet taken orally once daily and dupilumab a subcutaneous injection self-administered every other week.
- Labeling for dupilumab carries Warnings and Precautions for (1) hypersensitivity, (2) conjunctivitis and keratitis, (3) eosinophilic conditions, and (4) parasitic infections.[h] Labeling for abrocitinib will present Boxed Warnings for (1) serious bacterial, fungal, viral, and opportunistic infection (including tuberculosis), (2) all-cause mortality (including

[f] Sidbury R, *et al*. Guidelines of care for the management of atopic dermatitis. Part 3: Management and treatment with phototherapy and systemic agents. J Am Acad Dermatol. 2014;71(2):327-349.

[g] Abrocitinib Safety Update, submitted to NDA 213871 (eCTD 0008) on November 23, 2020.

[h] Prescribing Information for DUPIXENT® (dupilumab) injection, for subcutaneous use, 10/2021 (Revised), accessed at Drugs@FDA on October 25, 2021.

sudden cardiovascular death), (3) malignancies (including lymphoma and lung cancer), (4) MACE, and (5) pulmonary embolism and venous thrombosis.

- FDA labeling indicates dupilumab for "the treatment of patients aged 6 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable."[i] FDA labeling will restrict abrocitinib to patients (b) (4) "with *refractory* [*emphasis added*], moderate-to-severe atopic dermatitis whose disease is not adequately controlled with *other systemic drugs, including biologics* [*emphasis added*], or when use of those therapies is inadvisable."

These differences introduce strong potential for patient channeling that might severely challenge or possibly invalidate (non-randomized) observational studies seeking causal estimates of abrocitinib treatment effects. Despite these limitations, we assessed dupilumab (and the other comparator treatments considered) as **ARIA Sufficient** for signal refinement (the regulatory purpose for the post-market safety assessment required by DDD).

4 OUTCOMES

4.1 Outcomes of Interest

The motivating outcomes behind a possible post-market requirement include MACE, malignancies, and thrombosis. Other outcomes of concern include serious infections, opportunistic infections (including herpes zoster), hepatoxicity (including drug induced liver injury), and retinal detachment.

DDD defined MACE to include myocardial infarction (MI), stroke, cardiovascular death, and sudden cardiovascular death. FDA defines (1) myocardial infarction as "myocardial necrosis in a clinical setting consistent with myocardial ischemia," (2) stroke as an "acute episode of [typically persistent] focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction," (3) cardiovascular death as "death resulting from an acute myocardial infarction (MI), sudden cardiac death, death due to heart failure (HF), death due to stroke, death due to cardiovascular (CV) procedures, death due to CV hemorrhage, and death due to other CV causes," and (4) sudden cardiac death as "death that occurs unexpectedly and not within 30 days of an acute MI."[j,k]

The National Cancer Institute (NCI) defines malignancy as a disease "in which abnormal cells divide without control and can invade nearby tissues."[l] The NCI Surveillance, Epidemiology, and End Results (SEER) Program identifies primary-site tumors with malignant (invasive) potential by behavior code (NAACCR Item #523).[m]

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[i] Prescribing Information for DUPIXENT® (dupilumab) injection, *op. cit.*

[j] Hicks KA, *et al*. 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials. Circulation. 2018;137:961-972.

[k] With sudden cardiac death further defined by reference to seven clinical scenarios.

[l] National Cancer Institute, Dictionary of Cancer Terms, accessed at Definition of malignancy - NCI Dictionary of Cancer Terms - National Cancer Institute on October 27, 2021.

[m] Adamo M, Groves C, Dickie L, Ruhl J. (September 2021). SEER Program Coding and Staging Manual 2022. National Cancer Institute, Bethesda, MD 20892, accessed at SEER Program Coding and Staging Manual 2022 (cancer.gov) on October 27, 2021, pp 106-108.

Venous thromboembolism (VTE) includes deep vein thrombosis (DVT) and pulmonary embolism (PE). Criteria for definite DVT typically require confirmation by venography, duplex ultrasound, imaging (computerized tomography or magnetic resonance imaging), or autopsy.[n] Criteria for definite PE typically require confirmation by angiography, imaging, or pathology.[o]

4.2 Is ARIA sufficient to assess the outcomes of interest?

NO. The particular regulatory purpose for post-market assessment of abrocitinib safety requires accurate estimates of adverse event incidence. For study outcomes with low incidence (such as, MACE, malignancies, and VTE in the atopic dermatitis patient population), recent FDA Guidance for Real-World Data (*e.g.*, SDD) stresses the importance of identifying outcomes with both high specificity and high sensitivity.[p] Post-market studies using electronic healthcare data (such as, SDD) might accurately identify the outcomes of interest by complete verification of possible events initially ascertained by sensitive code search. Adequate verification typically requires standardized clinical review of primary patient records stored in paper or electronic medical record systems. An electronic healthcare data source linked to a suitable cancer registry might accurately identify patients with a newly recognized malignancy. However, ARIA capabilities currently exclude (1) clinical review of primary patient records for outcome verification and (2) SDD linkage to population-based cancer registries. In the particular regulatory context presented by abrocitinib NDA 213871, sufficient post-market assessment of ultra-rare and heterogenous outcomes (such as lymphoma) requires access to primary patient records for detailed characterization and accurate classification.

Complete capture of MACE requires a method for identifying sudden cardiac deaths that occur in settings outside the healthcare system. Post-market studies might accurately ascertain sudden cardiac deaths in an electronic healthcare data source if linked to a population-based mortality register (*e.g.*, U.S. National Death Index). However, ARIA capabilities currently exclude SDD linkage to the National Death Index.[q] In certain settings, OSE might accept one approach for assessing sudden cardiac death and entirely different approaches for assessing other MACE components. In the current regulatory context, sufficient assessment of MACE as a composite requires a uniform approach that assesses each of the MACE components with comparable rigor.

ARIA might identify VTE with sufficient specificity for some regulatory purposes.[r] In some clinical settings (*e.g.*, after orthopedic surgery), events operationally defined by coded information in an electronic healthcare data source might identify VTE with near perfect

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[n] Spencer FA, *et al*. The Worcester Venous Thromboembolism Study: a population-based study of the clinical epidemiology of venous thromboembolism. J Gen Intern Med. 2006;21:722-727.

[o] *Ibid*.

[p] Food and Drug Administration, September 2021, Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products, Draft Guidance for Industry, accessed at https://www.fda.gov/media/152503/download on October 27, 2021, , p19.

[q] OSE often cites incomplete capture of sudden cardiac death as a reason for determining ARIA Not Sufficient for MACE. For precedent, see, Liu W, *et al*., ARIA Sufficiency Memo for romosozumab (Evenity®), filed under BLA 761062 on March 18, 2019 (DARRTS Reference ID: 4405363).

[r] For precedent, see, Ajao A, *et al*., ARIA Sufficiency Memo for Levonorgestrel and Ethinyl Estradiol Transdermal System, filed under NDA 204017 on January 25, 2020 (DARRTS Reference ID: 4565904).

specificity (*i.e.*, positive predictive value approaching 100%).[s] However, OSE finds no evidence to support a determination that a highly specific operational definition might achieve the sensitivity required for accurate estimation of VTE incidence in the atopic dermatitis patient population.

Finally, poor patient retention in SDD limits the usefulness of ARIA for long latency outcomes (such as, malignancy).[t]

To address the regulatory purpose presented by abrocitinib treatment for atopic dermatitis, OSE finds **ARIA Not Sufficient** in the Outcomes domain. Sufficiency requires particularly rigorous methods for ascertaining and characterizing the motivating outcomes of concern (MACE, malignancies, and thrombosis) and any other serious adverse event regarded as appropriate for post-market assessment.

In summary, the particular regulatory purpose presented for post-market assessment of abrocitinib safety requires accurate estimates of adverse event incidence. Accurate estimation requires methods that identify outcomes with both high specificity and high sensitivity. ARIA algorithms for identifying the outcomes of concern generally have poor or unknown sensitivity and minimally acceptable category-wide specificity (e.g., lymphoma as a broad outcome class) but poor or unknown specificity for possibly important outcomes within a class (e.g., peripheral T-cell lymphoma).

A quantitative assessment conducted for this ARIA Sufficiency Memorandum indicated that ARIA using a highly specific and moderately sensitive method (75% sensitivity) might estimate incidence with accuracy sufficient for signal refinement. This quantitative assessment also indicated that ARIA with insensitive methods (<50% sensitivity) would underestimate incidence with a magnitude of error large enough to defeat the regulatory purpose for the post-market study required by DDD. Meaningful quantitative bias analysis (QBA) of ARIA results would require information currently unavailable about the sensitivity of ARIA methods for ascertaining MACE, malignancy, and thrombosis.

5 COVARIATES

5.1 Covariates of Interest

Table 5 lists covariates possibly important to data analysis and study interpretation. ARIA might use information about these covariates to conduct analyses in patient subgroups defined by sex, age, treatment history, and disease severity.

Table 5: Covariates of Interest

Safety Endpoint	Possibly Important Covariates
MACE	age, sex, history of hypertension, history of diabetes, history of

[s] Tamariz L, et al. A systematic review of validated methods for identifying venous thromboembolism using administrative and claims data. Pharmacoepidemiol Drug Saf. 2012;21 Suppl 1:154-162.

[t] OSE often cites poor long-term follow as a reason for determining ARIA Not Sufficient for malignancy. For precedent, see, Callahan C, *et al.*, ARIA Sufficiency Memo for mavenclad (Cladribine®), filed under NDA 022561 on March 20, 2020 (DARRTS Reference ID: 4406278).

	myocardial infarction or stroke (possible criterion for cohort exclusion), history of other cardiovascular disease, AD disease severity, and tobacco use history
Malignancy	age, sex, history of HIV/AIDS, organ transplantation, or autoimmune disease (possible criteria for cohort exclusion), AD disease severity, history of malignancy (possible criterion for cohort exclusion), and tobacco use history
Venous thrombo-embolism	age, sex, concomitant use of oral contraceptives (women only), AD disease severity, and history of thrombosis (possible criterion for cohort exclusion)

ABBREVIATION: AD – atopic dermatitis

5.2 Is ARIA sufficient to assess the covariates of interest?

YES. ARIA reliably captures patient sex and age. ARIA might credibly use diagnosis, procedure, and pharmacy codes in SDD to exclude patients with organ transplantation, autoimmune disease, HIV infection, or malignancy history.

Within limits imposed by the time-restricted historical patient record available in SDD, ARIA might credibly use diagnosis, procedure, and pharmacy codes in SDD to classify patients into subgroups defined by medical history. Cohort eligibility requiring 12-month pre-index enrollment in SDD should provide sufficient data capture for signal refinement.

ARIA offers no method for direct assessment of AD severity, a factor expected to determine exposure (abrocitinib or reference exposure) and possibly associated with one or more of the outcomes of interest. However, ARIA might use pre-index AD-specific treatments as a crude proxy for AD severity.[u] ARIA offers incomplete methods for assessing lifestyle risk factors (*e.g.*, tobacco use history). Despite these limitations, we assessed covariate capture as ARIA Sufficient for signal refinement.

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

ARIA might address the objectives for post-market assessment by conducting analyses in patient cohorts defined by age, index AD treatment, and pre-index medical history.

Applicable ARIA analytic tools permit descriptive (Level 1) and comparative (Level 2) analysis, as indicated below.

- Level 1 (Descriptive) Analysis
  - To determine exposure (number of exposed patients and patient-years at risk).
  - To calculate (background) incidence rates for the adverse events of interest in patients with moderate or severe atopic dermatitis.
- Level 2 (Comparative) Analysis

[u] Cho Y-T, *et al*. Prevalence of baseline comorbidities in patients with atopic dermatitis: A population-based cohort study in Taiwan. JAAD Int. 2020;1(1):50-58 (https://doi.org/10.1016/j.jdin.2020.05.002).

- Covariate Stratification – to calculate incidence rates for the adverse events of interest in patient cohorts defined by exposure (abrocitinib, broad reference, or narrow reference) and other covariates (age, sex, index year, and pre-index medical history).
- Propensity Score Analysis – to estimate an effect size with additional control for pre-index AD-specific treatments (as a proxy for AD severity).[v]

6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

YES. ARIA offers tools suited to the objectives for this post-market assessment. Post-market assessment in ARIA might proceed with a preliminary series of feasibility analyses (using Level 1 tools), followed later by a comparative analysis using the appropriate Level 2 tool (as determined by results from feasibility analysis) – Covariate Stratification or Propensity Score Analysis.

In a favorable setting, ARIA Propensity Score Analysis in SDD might produce a credible quantitative estimate for causal effect. Regardless of the analytic tool, however, conditions necessary for credible causal analysis in ARIA might not apply to post-market assessment of abrocitinib and the outcomes of interest. As discussed above, factors that limit ARIA include (1) concern about the suitability of dupilumab as an active comparator, (2) validity of algorithms available for identifying the outcomes of interest, and (3) absence of a direct method for assessing AD severity. Although these factors preclude ARIA from signal evaluation (to inform causality), we considered Propensity Score Analysis as a possibly useful tool for signal refinement, which is the regulatory purpose for this PMR.

7 NEXT STEPS

On October 5, 2021, OSE closed a series of Signal Assessment Meetings (SAMs conducted on September 13 and 23, 2021) and confirmed its determination of **ARIA Not Sufficient** by email exchanges with representatives from the OSE Sentinel Core Team, OSE Division of Epidemiology I (DEPI), OSE Division of Pharmacovigilance I, and OND Division of Dermatology and Dentistry (DDD).[w]

Upon approval of NDA 213871, DDD will issue a FDAAA Post-Marketing Requirement (PMR) for a study fitting the following description.

Conduct a prospective observational study (analyses conducted in patient cohorts enrolled prospectively and followed actively in accordance with a written protocol) to assess the long-term safety of abrocitinib treatment in U.S. adult patients with moderate-to-severe atopic dermatitis. Fully ascertain and centrally verify serious adverse events, Major Adverse Cardiovascular Events (myocardial infarction, stroke, cardiovascular death, and sudden death), malignancies (including lymphoma, lung cancer, and other malignancies), serious infections, opportunistic infections (including herpes zoster), retinal detachment, thrombosis (including deep venous thrombosis, pulmonary embolism and arterial thrombosis), hepatoxicity (including drug induced liver injury), and

[v] Methods available in ARIA for Propensity Score Analysis include matching, stratification, inverse probability of treatment weighting (IPTW), and stratum weighting.

[w] Bui Nguyen T, October 5, 2021 (email), FW: INPUT NEEDED - VIRTUAL SIGNAL SAFETY ASSESSMENT - Abrocitinib NDA 213871, filed in RM Client as [FW_ INPUT NEEDED - VIRTUAL SIGNAL SAFETY ASSESSMENT - Abrocitinib NDA 213871.pdf] on December 15, 2021 (Object ID: 090026fc8039ac0b).

possibly other adverse events of special interest. For each adverse-event outcome separately, compare incidence in abrocitinib -treated patients against reference rates internally derived from analyses conducted in patients treated with dupilumab or other chronic systemic treatments for moderate-to-severe atopic dermatitis. Regardless of treatment discontinuation or switch to a different treatment for atopic dermatitis, continue following patients for malignancy outcomes and possibly other adverse events with delayed onset. Enroll a sufficient number of patients to describe the frequency of the adverse events of special interest in representative U.S. patients who start treatment with abrocitinib for atopic dermatitis in the setting of routine clinical practice. Implement a plan that uses rigorous, transparent, and verifiable methods to ascertain and characterize safety events that occur during and after treatment with abrocitinib. Enroll patients over a 4-year period and follow each patient for at least 8 years from time of enrollment.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: November 22, 2021

To: Gary Chiang**,** MD, Clinical Reviewer,
Division of Dermatology and Dentistry (DDD)
David Kettl, MD, Clinical Team Leader, DDD
Dawn Williams, Regulatory Project Manager, DDD

From: Laurie Buonaccorsi, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, Team Leader, OPDP

Subject: OPDP Labeling Comments for CIBINQO™ (abrocitinib tablets), for oral use (Cibinqo)

NDA: 213871

In response to DDD's initial consult request dated October 23, 2020, OPDP provided a review of the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original NDA submission for Cibinqo on March 16, 2021. After substantial revisions to the PI and Medication Guide, DDD requested additional comments on the proposed labeling.

Labeling

PI: OPDP's comments on the proposed labeling are based on the revised draft PI, Sharepoint version dated November 22, 2021, and are provided below.

Medication Guide: A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide are based on the revised PI, Sharepoint version dated November 22, 2021, and are provided below.

Thank you for your consult. If you have any questions, please contact Laurie Buonaccorsi at (240) 402-6297 or laurie.buonaccorsi@fda.hhs.gov.

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LAURIE J BUONACCORSI
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 17, 2021
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 213871
Product Name and Strength:	Cibinqo (abrocitinib) tablet, 50 mg, 100 mg and 200 mg
Applicant/Sponsor Name:	Pfizer Inc.
OSE RCM #:	2020-1836-1
DMEPA 1 Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels received on March 1, 2021 for Cibinqo. Division of Dermatology and Dentistry (DDD) requested that we review the revised container labels for Cibinqo (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

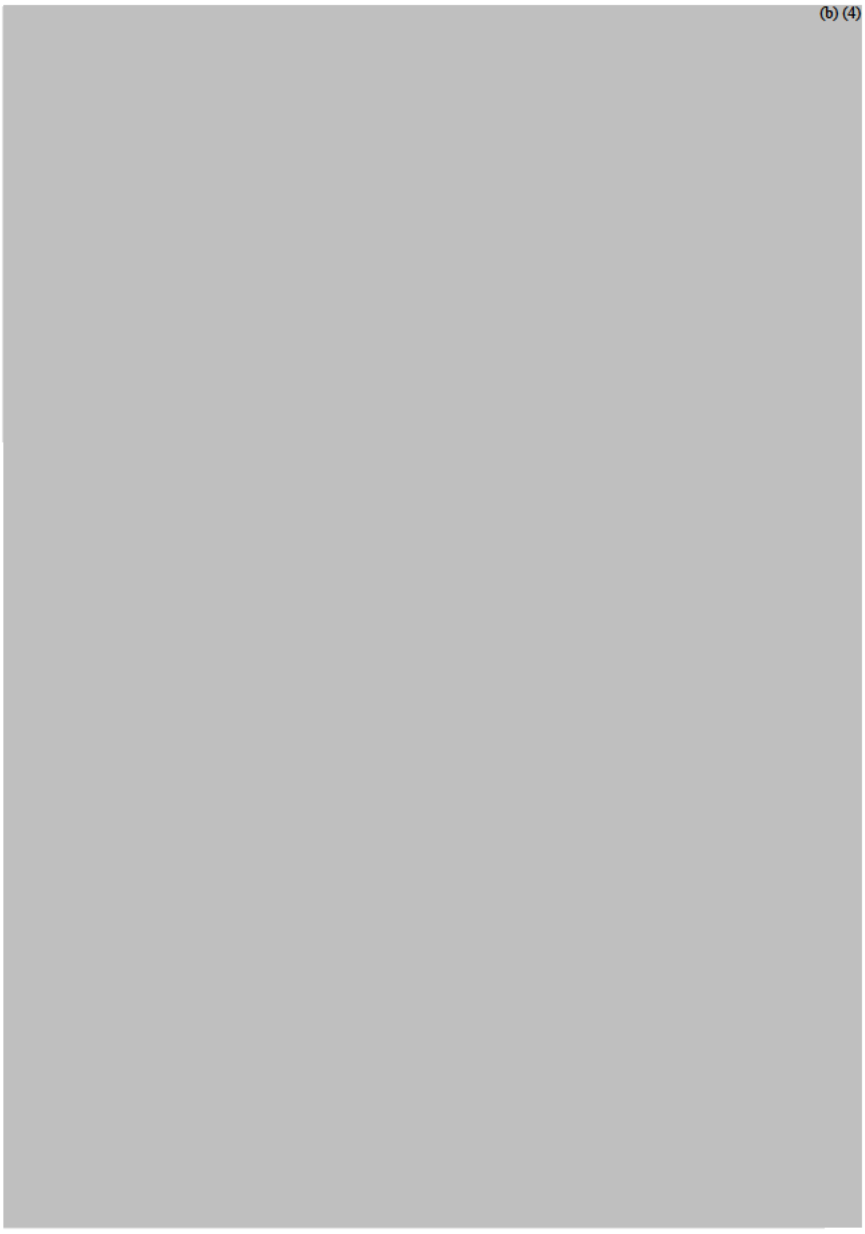
[a] Patel, M.. Label and Labeling Review for abrocitinib (NDA 213871). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 DEC 2. RCM No.: 2020-1836.

(b) (4)

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON MARCH 1, 2021

- **Container labels and Carton labeling available in EDR at: \\CDSESUB1\evsprod\NDA213871\0021\m1\us**

A. Container labels



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SEVAN H KOLEJIAN
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Clinical Inspection Summary (CIS)

Date	April 21, 2021
From	John Lee, M.D., Medical Officer Phillip Kronstein, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE)
To	Dawn Williams, Regulatory Project Manager Gary Chiang, M.D., Medical Officer David Kettl, M.D., Clinical Team Leader Division of Dermatology and Dentistry (DDD)
Application	NDA 213871
Applicant	Pfizer, Inc.
Drug	Abrocitinib
NME / Original NDA	Yes
Review Timeframe	Priority
Proposed Indication	Treatment of moderate or severe atopic dermatitis
Consultation Date	September 28, 2020
CIS Goal Date	February 24, 2021 (original); April 25, 2021 (extended)
Action Goal Date	April 25, 2021
PDUFA Due Date	April 25, 2021

I. OVERALL ASSESSMENT OF FINDINGS

Two clinical investigators were selected for good clinical practice (**GCP**) inspection. A remote regulatory assessment (**RRA**) was performed in lieu of an on-site GCP inspection for one of the two CI sites due to the on-going COVID-19 pandemic-related travel restrictions. Overall, no significant GCP violations were identified. Based on the results of the inspection and the RRA, the clinical data generated by the two CIs appear to be supportive of this NDA.

It should be noted that, at Site 1002 in Study B7451012 (Iftikhar Hussain; Tulsa, Oklahoma), the observations included violations of EASI (Eczema Area and Severity Index, 4 subjects) or pruritis NRS (Numerical Rating Scale, one subject) study eligibility criteria. The violations allowed subjects with disease severity scores that are not high enough to be enrolled in study. The violations were reported in the NDA for all 5 subjects. Enrolling subjects with less severe disease than that allowed by the protocol appeared to work against the demonstration of abrocitinib efficacy.

II. BACKGROUND

This NDA from Pfizer, Inc. is in support of abrocitinib (PF-04965842) for treating atopic dermatitis (**AD**). The NDA has been granted Breakthrough Therapy, Fast Track, Rolling Review, and Priority Review designations.

AD is a common inflammatory skin disorder characterized by flaky lesions and intense pruritus, often life-long with recurrent debilitating flares. Mild or moderate AD is typically managed using topical agents, initially with emollients and/or corticosteroids. More severe AD cases often require systemic corticosteroids and/or other therapies including ultraviolet phototherapy and/or immunomodulation using biologics (e.g., interferon or monoclonal antibody) or cytotoxic agents (e.g., methotrexate or azathioprine). Cell signal transduction triggered by cytokine binding to the Janus kinase 1 (**JAK1**) receptor appears to be important to the pathophysiology of AD.

Abrocitinib is an orally active small molecule that selectively inhibits cytokine activation of JAK1. The sponsor claims that the efficacy and safety of abrocitinib as a new therapeutic agent for AD are well supported by the following two Phase 3 randomized controlled studies, nearly identical in design and sharing the same study title. The common primary study objective was to evaluate the efficacy and safety of abrocitinib in subjects of age $\geq$ 12 years (body weight $\geq$ 40 kg) with moderate/severe AD. Both studies were identified for audit in support of this NDA review, at either an on-site GCP inspection or by RRA. The two studies are described together below.

Studies B7451012 and B7451013

A Phase 3 Randomized, Double-Blind, Placebo-controlled, Parallel Group, Multi-Center Study to Evaluate the Efficacy and Safety of PF-04965842 Monotherapy in Subjects Aged 12 Years and Older, with Moderate to Severe Atopic Dermatitis

Study B7451012 was conducted between 2017-2019 in 387 subjects at 69 CI sites in 8 countries (US, Canada, and Europe). Study B7451013 was conducted between 2018-2019 in 391 subjects at 102 CI sites in 13 countries (US, Canada, Australia, Europe, and

East Asia). Following a wash-out period of any previous AD therapies, eligible subjects with refractory AD were randomized (2/2/1, respectively) to 200 or 100 mg abrocitinib or placebo, once daily for 12 weeks. Randomization was stratified by age and AD severity. Subjects either continued in a long-term extension study (B7451015) after 12 weeks of study treatment or were evaluated for safety during four weeks of follow up. The major efficacy evaluations were:

- Co-primary endpoints: Week 12 observations of 0 (clear) or 1 (almost clear) scores on Investigator Global Assessment (**IGA**) with reduction from baseline of $\geq$ 2 points, and 75% improvement in Eczema Area and Severity Index (**EASI-75**)
- Major secondary endpoints: (a) Improvement by $\geq$ 4 points in pruritus numerical rating scale (**NRS**) at Weeks 2, 4, and 12; (b) Week 12 improvement in Pruritus and Symptoms Assessment for Atopic Dermatitis (**PSAAD**)

III. INSPECTION RESULTS

1. Lisa Usdan, M.D.

6401 Poplar Avenue
Memphis, Tennessee 38119
Inspection dates: March 2-4, 2021

Study B7451013, Site 1030: Nine subjects were enrolled and 8 completed the study. One subject withdrew from the study after an adverse event (**AE**). Case records were reviewed in detail for all subjects.

No significant GCP deficiencies were observed. Study files and subject case records were well maintained and readily available for review. No unreported AEs or unreported protocol deviations were discovered. The primary and secondary efficacy endpoint data were verifiable against the data reported in the NDA.

2. Iftikhar Hussain, M.D.

7307 South Yale Avenue
Tulsa, Oklahoma 74136
Inspection dates: April 12-16, 2021

The audit of Study B7451012 at this Site 1002 was conducted by RRA, by video conferencing and electronic document sharing. The RRA consisted of: informed consent, subject selection, study therapy, endpoint assessment, subject case records review, protocol compliance, and recordkeeping. Sixteen subjects were enrolled and all completed the study. Case records were reviewed in detail for all subjects.

No significant GCP deficiencies were observed. Notable deficiency observations included violations of study eligibility criteria for 5 subjects, not meeting either the EASI-75 criterion (4 subjects) or the pruritis NRS criterion (one subject). For all subjects (violations), the disease severity scores were not high enough to meet the study inclusion criteria. All 5 violations were reported in the NDA. Enrolling subjects with less severe disease than that allowed by the protocol appeared to work against the demonstration of abrocitinib

efficacy. No unreported clinical AEs were discovered. The primary and secondary efficacy endpoint data were verifiable against the data reported in the NDA.

NOTE: For both CI sites, the establishment inspection report (**EIR**) or the RRA report has not been received from the field office and the results reported in this CIS are based on preliminary communication with the field investigator. Upon receipt and review of the EIR or the RRA report, any new significant finding will be reported to the review division in an addendum to this CIS.

{See appended electronic signature page}

John Lee, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

{See appended electronic signature page}

Phillip D. Kronstein, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

Central Document Room / NDA 213871
DDDP / Team Leader / David Kettl
DDDP / Medical Officer / Gary Chiang
DDDP / Regulatory Project Manager / Dawn Williams
OSI / Office Director / David Burrow
OSI / DCCE / Division Director / Ni Khin
OSI / DCCE / GCPAB / Branch Chief / Kassa Ayalew
OSI / DCCE / GCPAB / Team Leader / Phillip Kronstein
OSI / DCCE / GCPAB / Medical Officer / John Lee
OSI / DCCE / GCPAB / Program Analyst / Yolanda Patague
OSI / Database Project Manager / Dana Walters

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: March 22, 2021 **Date consulted:** March 4, 2021

From: Jean Limpert, MD, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Miriam Dinatale, DO, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Dermatology and Dentistry (DDD)

Drug: Cibinqo (abrocitinib) tablets

NDA: 213871

Applicant: Pfizer, Inc.

Subject: Pregnancy and Lactation Labeling

Proposed Indication: Treatment of (b) (4) adults with moderate to severe atopic dermatitis (AD)

Materials Reviewed:

- DPMH consult request dated March 4, 2020, DARRTS reference ID 4756811
- Applicant's submitted background package and proposed labeling for NDA 213871, submitted August 25, 2020

- DPMH review for Postmarketing Requirements (PMRs) for Cibinqo (abrocitinib), NDA 213871, January 14, 2021, Jean Limpert, MD, Medical Officer, DARRTS reference ID 4735395
- DPMH labeling review for Olumiant (baricitinib), NDA 207924, February 5, 2021, Jean Limpert, MD, Medical Officer, DARRTS reference ID 4742935[1]
- DPMH labeling review for drug Xeljanz (tofacitinib), NDA 203214, March 20, 2018, Jane Liedtka MD, Medical Officer, DARRTs reference ID: 4236947[2]

Consult Question: "We request your assistance/recommendations regarding the PLLR language in the proposed label."

INTRODUCTION AND BACKGROUND

On August 25, 2020, Pfizer Inc. submitted an original new drug application (NDA) for abrocitinib, a new molecular entity. The proposed indication is the treatment of moderate to severe A (b) (4)

On December 22, 2020, DDD consulted DPMH to provide input for PMRs. On March 4, 2021, DDD consulted DPMH to provide input for the PLLR subsections of labeling.

Regulatory History

- Abrocitinib has been developed as an oral treatment for AD. Abrocitinib was granted Breakthrough Therapy Designation in February 2018.
- Abrocitinib is an orally bioavailable small molecule that selectively inhibits JAK1 by blocking the ATP binding site. JAKs phosphorylate and activate Signal Transducers and Activators of Transcription (STATs). Many of the cytokines that mediate the immune response in AD signal through the JAK/STAT pathway.
- While there are no JAK inhibitors approved for the treatment of moderate to severe AD, there are other JAK inhibitors currently under review by DDD.
- There are three JAK inhibitors approved for the treatment of moderate to severe rheumatoid arthritis (i.e., Olumiant (baricitinib) NDA 207924, Xeljanz (tofacitinib) NDA 203214, and Rinvoq (upadacitinib) NDA 211675).
- The JAK pathway is involved in cell adhesion and cell polarity which can affect early embryonic development. Animal data for the class of JAK inhibitors indicates varying degrees of embryofetal toxicity including embryofetal toxicity warnings for some drugs in the class (e.g., upadacitinib).
- Dupilumab is the first and only systemic biologic product (i.e., human monoclonal IgG4 antibody) currently approved for the treatment for moderate to severe AD.

Drug Characteristics[3]

- Proposed dosing: 100 mg orally once daily

[1] The Olumiant review was part of the materials reviewed but was not a source relied upon for the labeling recommendations in this consult review

[2] The Xeljanz review was part of the materials reviewed but was not a source relied upon for the labeling recommendations in this consult review

[3] DPMH PMR review for drug Cibinqo (abrocitinib), NDA 213871, Jean Limpert, MD, Medical Officer, DARRTs reference ID: 4735395

- Bioavailability: 64%, protein binding of active metabolites M1 and M2 are 37% and 29%
- Mean elimination half-life of abrocitinib and its two active metabolites: 3-5 hours
- Molecular weight: 323.4 Daltons
- Adverse reactions from clinical trials: nausea, headache, acne, herpes simplex, vomiting, dizziness, and increase in blood creatinine phosphokinase
- Based on adverse reactions observed in clinical trials, there is a potential risk of serious infections, malignancy, retinal detachment, and thrombosis

REVIEW

PREGNANCY

Atopic Dermatitis and Pregnancy[4]

It is estimated up to 10% of adults in the United States are affected by AD though prevalence estimates are limited and vary because AD is a clinical diagnosis.[5] For adults with AD, an estimated 44-57% have moderate disease and 12-21% have severe disease. Approximately half of the AD population are females and AD affects all age groups including females of reproductive potential.[6] In about half of cases, AD may worsen during pregnancy and untreated AD may put a pregnant person at risk for infections (e.g., eczema herpeticum, *Staphylococcus aureus* infections).[7] Some atopic diseases are associated with decreased fertility, but the relationship for AD and reduced fertility is less clear.[8,9]

Initial therapies include topical treatments and phototherapy. Systemic therapies are recommended when AD is not adequately controlled by these initial therapies and are typically needed for patients with moderate to severe AD. There are currently two approved systemic therapies for patients with moderate-severe AD (i.e., systemic corticosteroids and dupilumab). Systemic corticosteroids can be effective for severe acute exacerbations but are not recommended for long-term use. Use of systemic corticosteroids during pregnancy may result in adverse effects including elevated blood pressure, glucose intolerance, susceptibility to infection, and fetal growth restriction. Dupilumab is an injectable systemic IgG4 monoclonal antibody.

[4] DPMH labeling review for drug Cibinqo (abrocitinib), NDA 213871, Jean Limpert, MD, Medical Officer, DARRTs reference ID: 4735395

[5] Chiesa Fuxench ZC, Block JK, Boguniewicz M, et al. Atopic Dermatitis in America Study: a cross-sectional study examining the prevalence and disease burden of atopic dermatitis in the US adult population. *J Invest Dermatol.* 2019;139(3):583-590.

[6] Heilskov, S., Deleuran, M.S. & Vestergaard, C. Immunosuppressive and Immunomodulating Therapy for Atopic Dermatitis in Pregnancy: An Appraisal of the Literature. *Dermatol Ther (Heidelb)* **10,** 1215–1228 (2020).

[7] Napolitano M, Ruggiero A, Fontanella G, Fabbrocini G, Patruno C. New emergent therapies for atopic dermatitis: A review of safety profile with respect to female fertility, pregnancy, and breastfeeding. Dermatol Ther. 2021 Jan;34(1):e14475.

[8] Langan, S.M.; Irvine, A.D.; Weidinger, S. Atopic dermatitis. Lancet 2020, 396, 345–360.

[9] Napolitano M, Ruggiero A, Fontanella G, Fabbrocini G, Patruno C. New emergent therapies for atopic dermatitis: A review of safety profile with respect to female fertility, pregnancy, and breastfeeding. Dermatol Ther. 2021 Jan;34(1):e14475.

Current data in pregnancy are limited to one case report and limited cases in clinical trials, but there are no known safety issues for use during pregnancy. [10,11,12]

Nonclinical Experience

In embryo-fetal development studies, oral administration of abrocitinib to pregnant rats and rabbits during organogenesis at doses 31 or 11 times the maximum recommended human dose (MRHD), respectively, resulted in maternal dystocia and skeletal variations of short 13th ribs in rats and no adverse effects in rabbits. In higher doses in rats (48 times MRHD), increased embryofetal lethality and additional skeletal variations (cervical arches with reduced ventral processes, thickened ribs, and unossified metatarsals) were noted.

In a prenatal and postnatal development study, abrocitinib was administered orally to pregnant rats at doses of 10, 30, and 60 mg/kg/day beginning on gestation day 6 and continuing through lactation day 21. Dystocia with prolonged parturition and reduced offspring body weights were noted at 30 mg/kg/day (31 times the MRHD based on AUC comparison). Postnatal survival was markedly decreased at 60 mg/kg/day (48 times the MRHD based on AUC comparison). No maternal toxicity was observed at 10 mg/kg/day (6.9 times the MRHD based on AUC comparison). No abrocitinib-related effects on postnatal developmental, neurobehavioral, or reproductive performance of offspring was noted at doses up to 30 mg/kg/day (31 times the MRHD based on AUC comparison).

Reviewer comment: While other JAK inhibitors have caused skeletal malformations in nonclinical studies at clinically relevant exposures, abrocitinib did not cause skeletal malformations in rats or rabbits. While skeletal variations were noted at 31 times the MRHD, these variations correct with further growth and are not considered malformations.[13]

The reader is referred to the full Pharmacology/Toxicology review (currently pending) by John Dougherty, PhD.

Review of Human Pregnancy Data

The applicant conducted six studies in the AD clinical development program (n=3,120; n=2,856 exposed to abrocitinib). As of April 22, 2020, there have been ten cases of pregnancies reported in subjects exposed to abrocitinib in the AD clinical program.[14] Of these, there were seven maternal exposures and three paternal exposures. For the maternal exposures, two cases resulted in miscarriage and five cases had unknown outcomes. For the paternal exposures, one outcome was a full-term live birth and two cases had unknown outcomes.

Miscarriages (n=2):

[10] Kage P, Simon JC, Treudler R. A case of atopic eczema treated safely with dupilumab during pregnancy and lactation. J Eur Acad Dermatol Venereol. 2020:34(6):e256–7.
[11] Heilskov, S., Deleuran, M.S. & Vestergaard, C. Immunosuppressive and Immunomodulating Therapy for Atopic Dermatitis in Pregnancy: An Appraisal of the Literature. *Dermatol Ther (Heidelb)* **10,** 1215–1228 (2020).
[12] DPMH labeling review for Dupixent, BLA 761055, January 13, 2017, Christos Mastroyannis, MD, Medical Officer, DARRTs reference ID: 4041992
[13] Information based on email correspondence with Barbara Hill, 3/18/21
[14] Applicant's Summary of Clinical Safety, pages 220-221

- 27-year-old woman with atopic dermatitis had a spontaneous abortion at approximately 3.5 weeks' gestation. The patient had been on abrocitinib 200 mg daily for 84 days. Concomitant medications were dermasil lotion and ibuprofen for tooth ache. The investigator considered the event unrelated to the study drug.
- 19-year-old woman with atopic dermatitis had a spontaneous abortion at approximately 3.5 weeks gestation. The patient had been on abrocitinib 200 mg daily for 58 days. The mother consumed alcohol but was not taking concomitant medications. The investigator and sponsor considered the event not related.

Reviewer comment: Five out of seven cases of exposure during pregnancy have unknown outcomes. Spontaneous abortions occurred in two cases. One of the cases was confounded by alcohol use and in the other case it is not possible to determine if abrocitinib was casually related. No safety conclusions can be drawn based on the data.

While the sponsor provided pregnancy outcome information for paternal exposures, these data do not inform the risk of exposure of abrocitinib during pregnancy. Additionally, there are no concerns for genotoxicity that would make the results from paternal exposures relevant.

Review of Literature

Applicant's Review of Literature

DPMH Review of Literature

DPMH performed a search in PubMed, Embase, Micromedex, [15] TERIS, [16] Reprotox, [17] and Briggs[18] to find relevant articles related to the use of abrocitinib during pregnancy Search terms included "abrocitinib" AND "pregnancy," "pregnant women," "birth defects," "congenital malformations," "stillbirth," "spontaneous abortion," "miscarriage," and "fetal loss." Abrocitinib was not referenced in the databases.

A 2021 review article summarized new therapies for atopic dermatitis including JAK inhibitors. No published data for abrocitinib in pregnant persons were identified. The review article states the following about JAK inhibitors: "data about their effect on human fertility and pregnancy are still poor. However, data from animal seem to suggest that they could have some potential effects on fetal development and pregnancy outcomes."[19]

LACTATION

Nonclinical Experience

Lactating female rats were orally administered a single dose of 10 mg/kg abrocitinib on lactation day 12. Abrocitinib AUC was approximately 5 times greater in milk than in plasma.

[15] https://www.micromedexsolutions.com, accessed 3/16/21

[16] Truven Health Analytics information. Teris, accessed 3/16/21

[17] Truven Health Analytics information. Reprotox, accessed 3/16/21

[18] Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 10th edition. 2015, Philadelphia, PA. online, accessed 3/16/21

[19] Napolitano M, Ruggiero A, Fontanella G, Fabbrocini G, Patruno C. New emergent therapies for atopic dermatitis: A review of safety profile with respect to female fertility, pregnancy, and breastfeeding. Dermatol Ther. 2021 Jan;34(1):e14475.

The reader is referred to the full Pharmacology/Toxicology review (currently pending) by John Dougherty, PhD.

Review of Pharmacovigilance Database
The applicant did not identify any cases related to lactation.

Review of Literature
Applicant's Review of Literature
The applicant reports did not identify data on the presence of abrocitinib in human milk, the effects in the breastfed infant, or the effects on milk production.

DPMH review of literature
This Reviewer performed a search in PubMed, Embase, Micromedex,[20] TERIS, [21] Reprotox, [22] and Briggs, [23] *Medications and Mothers' Milk,*[24] and LactMed[25] to find relevant articles related to the use of abrocitinib during lactation. Search terms included "abrocitinib" AND "breastfeeding" or "lactation." Abrocitinib was not referenced in the databases and no published data were identified.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL
Nonclinical Experience
Abrocitinib impaired female fertility at 70 mg/kg/day (84 times the MRHD based on AUC comparison). Impaired fertility in female rats reversed 1 month after cessation of abrocitinib administration. Abrocitinib did not impair male fertility at doses up to 70 mg/kg/day (76 times the MRHD based on AUC comparison).

In a 2-year oral carcinogenicity study in rats, abrocitinib increased the incidence of benign thymomas in female rats at doses of 10 and 30 mg/kg/day (8.1 and 41 times the MRHD, respectively, based on AUC comparison). Abrocitinib was not carcinogenic in female rats at 3 mg/kg/day (1.7 times the MRHD based on AUC comparison) or male rats at doses up to 30 mg/kg/day (41 times the MRHD based on AUC comparison). Abrocitinib was not carcinogenic in Tg.rasH2 mice at oral doses up to 60 mg/kg/day in males and 75 mg/kg/day in females.

Abrocitinib was not mutagenic in the Ames assay. Although abrocitinib was aneugenic in the in vitro TK6 micronucleus assay, abrocitinib was not aneugenic or clastogenic in an in vivo rat bone marrow micronucleus assay.

Reviewer comment: The findings were discussed with the Pharmacology/Toxicology team. Abrocitinib does not appear to be genotoxic at clinically relevant concentrations.

[20] https://www.micromedexsolutions.com, accessed 3/16/21
[21] Truven Health Analytics information. Teris, accessed 3/16/21
[22] Truven Health Analytics information. Reprotox, accessed 3/16/21
[23] Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 10th edition. 2015, Philadelphia, PA. online, accessed 3/16/21
[24] https://www.halesmeds.com, accessed 3/16/21
[25] https://www.ncbi.nlm.nih.gov/books/NBK501922/, accessed 3/16/21

The reader is referred to the full Pharmacology/Toxicology review (currently pending) by John Dougherty, PhD.

Review of Pharmacovigilance Database
The applicant did not identify any cases related to fertility in males and females of reproductive potential.

Review of Literature
Applicant's Review of Literature
The applicant did not identify any literature related to fertility.

DPMH review of literature
This Reviewer performed a search in PubMed, Embase, Reprotox to find relevant articles related to the use of abrocitinib and effects on fertility. Search terms included "abrocitinib" AND "fertility," "infertility," "contraception," and "oral contraceptives."

Wang et al[26] conducted an in vitro assessment of cytochrome P450 3A inhibition of abrocitinib in healthy participant and found there was an absence of induction effect of abrocitinib on oral contraceptives.

DISCUSSION AND CONCLUSIONS
Pregnancy
AD is a common disease that affects up to 10% of adults and of those affected, it is likely more than half of these adults have moderate-severe disease for which systemic immunomodulators may be needed, including in females of reproductive potential.

There are currently no published data on abrocitinib use in pregnancy. In clinical trials, pregnant persons were excluded, and females of reproductive potential were expected to use effective contraception. Pregnancy outcome data from clinical trials includes seven maternal exposures, including two miscarriages and five unknown outcomes. Pregnancy outcome information was not consistently collected for women who became pregnant in the clinical trials and the available human data are not adequate to assess the safety of abrocitinib use in pregnancy.

Nonclinical studies have demonstrated varying degrees of embryofetal toxicity within the class of JAK inhibitors. In animal reproduction studies, oral administration of abrocitinib to pregnant rats and rabbits during organogenesis at doses 11 and 31 the MRHD resulted in skeletal variations that were not considered significant. In addition, dystocia with prolonged parturition were noted in rat studies. Adverse findings occurred at multiples that are less concerning compared to the nonclinical findings across the spectrum of JAK inhibitors.

Given the anticipated use of abrocitinib in females of reproductive potential who may become pregnant, and the limited information collected in the clinical trials to date, DPMH recommends PMRs for a pregnancy registry and complementary study. See January 14, 2021 DPMH review

[26] Wang, X. (2020). 15433 Assessment of cytochrome P450 3A inhibition and induction of abrocitinib: Midazolam drug-drug interaction (DDI) study and oral contraceptive DDI study. *Journal of the American Academy of Dermatology.*, *83*(6), AB151.

for postmarketing studies for Cibinqo (NDA 213871, DARRTS reference ID 4735395) for full details.

Lactation
There are no available clinical data regarding the presence of abrocitinib in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. Abrocitinib is transferred into the milk of lactating rats. Due to the potential risks of serious adverse reactions in adult patients taking abrocitinib (e.g., serious infections, malignancy, and thrombosis), breastfeeding is not recommended during treatment and for at least one day after the last dose of abrocitinib. DPMH also recommends a PMR for a clinical lactation study. See January 14, 2021 DPMH review for postmarketing studies for Cibinqo (NDA 213871, DARRTS reference ID 4735395) for full details.

Females and Males of Reproductive Potential
There are no human data with respect to the fertility. Nonclinical data suggest abrocitinib may reversibly impair fertility in female rats.

The nonclinical data do not suggest embryofetal toxicity at clinically relevant doses . Pregnancy testing and contraception recommendations are not recommended based on the available data.

LABELING RECOMMENDATIONS
DPMH revised subsections 8.1, 8.2, 8.3 and 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION
----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Advise not to breastfeed (8.2)

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Exposure Registry
There will be a pregnancy exposure registry that monitors pregnancy outcomes in pregnant persons exposed to CIBINQO during pregnancy. Pregnant persons exposed to CIBINQO and health care providers are encouraged to call Pfizer, Inc at (XXX) XXX-XXXX.

Risk Summary
Available data from pregnancies reported in clinical trials with CIBINQO are not sufficient to establish a drug-associated risk for major birth defects, miscarriage, or other adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of abrocitinib to pregnant rats and rabbits during organogenesis at doses 31 or 11 times the maximum recommended human dose (MRHD), respectively, resulted in maternal dystocia and skeletal variations in rats and no

adverse effects in rabbits *(see Data)*.

The estimated background risks of major birth defects and miscarriage for the indicated population are unknown. All pregnancies carry some risk of birth defects, loss, or other adverse outcomes. The background risks in the U.S. general population of major birth defects and miscarriages are 2-4% and 15-20% of clinically recognized pregnancies, respectively.

Data

Animal Data

In an embryofetal development study, abrocitinib was administered orally to pregnant rats at doses of 10, 30, or 60 mg/kg/day during the period of organogenesis. No fetal malformations were observed. Abrocitinib increased the incidence of skeletal variations of short 13th ribs at 30 mg/kg/day (31 times the MRHD based on AUC comparison). Increased embryofetal lethality and additional skeletal variations (cervical arches with reduced ventral processes, thickened ribs, and unossified metatarsals) were noted at 60 mg/kg/day (48 times the MRHD based on AUC comparison).

In an embryofetal development study, abrocitinib was administered orally to pregnant rabbits at doses of 10, 30, or 75 mg/kg/day during the period of organogenesis. No abrocitinib-related maternal or developmental toxicity was noted at doses up to 75 mg/kg/day (11 times the MRHD based on AUC comparison).

In a prenatal and postnatal development study, abrocitinib was administered orally to pregnant rats at doses of 10, 30, and 60 mg/kg/day beginning on gestation day 6 and continuing through lactation day 21. Dystocia with prolonged parturition and reduced offspring body weights were noted at 30 mg/kg/day (31 times the MRHD based on AUC comparison). Postnatal survival was markedly decreased at 60 mg/kg/day (48 times the MRHD based on AUC comparison). No maternal toxicity was observed at 10 mg/kg/day (6.9 times the MRHD based on AUC comparison). No abrocitinib-related effects on postnatal developmental, neurobehavioral, or reproductive performance of offspring was noted at doses up to 30 mg/kg/day (31 times the MRHD based on AUC comparison).

8.2 Lactation

Risk Summary

There are no data on the presence of abrocitinib in human milk, the effects on the breast-fed infant, or the effects on milk production. Abrocitinib was present in the milk of lactating rats (*see Data*). When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because of the serious adverse findings in adults, including risks of serious infections, malignancy, and thrombosis, advise women not to breastfeed during treatment with CIBINQO and for one day after the last dose (approximately 5-6 elimination half-lives).

Data

Lactating female rats were orally administered a single dose of 10 mg/kg abrocitinib on lactation day 12. Abrocitinib AUC was approximately 5 times greater in milk than in plasma.

8.3 Females and Males of Reproductive Potential

Infertility

Females

Based on the findings in rats, oral administration of CIBINQO may impair female fertility. Impaired fertility in female rats was reversible 1 month after cessation of abrocitinib oral administration *[see Nonclinical Toxicology (13.1)]*.

17 PATIENT COUNSELING INFORMATION

Pregnancy Registry

Advise patients to report their pregnancy to Pfizer, Inc. at XXX-XXX-XXXX *[see Use in Specific Populations (8.1)]*.

Lactation

Advise a patient not to breastfeed during treatment with CIBINQO and for one day after the last dose *[see Use in Specific Populations (8.2)]*.

Infertility

Advise females of reproductive potential that CIBINQO may impair fertility *[see Use in Specific Populations (8.3)]*.

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/s/

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LYNNE P YAO
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	March 22, 2021
To:	Dawn Williams, BSN Regulatory Project Manager **Division of Dermatology and Dentistry (DDD)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Ruth Mayrosh, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Laurie Buonaccorsi, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	CIBINQO (abrocitinib)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 213871
Applicant:	Pfizer Inc.

1 INTRODUCTION

On June 29, 2020 and August 25, 2020, Pfizer Inc. submitted for the Agency's review Part 1 and Part 2, respectively, of their rolling New Drug Application (NDA) 213871 for CIBINQO (abrocitinib) tablets. The proposed indication for CIBINQO (abrocitinib) tablets is for the treatment of moderate-to-severe atopic dermatitis (b) (4) (b) (4)

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Dermatology and Dentistry (DDD) on October 23, 2020 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for CIBINQO (abrocitinib) tablets.

2 MATERIAL REVIEWED

- Draft CIBINQO (abrocitinib) tablets MG received on August 25, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 5, 2021.
- Draft CIBINQO (abrocitinib) tablets Prescribing Information (PI) received on August 25, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 5, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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LAURIE J BUONACCORSI
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SHARON R MILLS
03/22/2021 03:57:36 PM

LASHAWN M GRIFFITHS
03/22/2021 03:58:44 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: March 16, 2021

To: Gary Chiang**,** MD, Clinical Reviewer,
Division of Dermatology and Dentistry (DDD)
David Kettl, MD, Clinical Team Leader, DDD
Dawn Williams, Regulatory Project Manager, DDD

From: Laurie Buonaccorsi, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, Team Leader, OPDP

Subject: OPDP Labeling Comments for abrocitinib tablets, for oral use

NDA: 213871

In response to DDD's consult request dated October 23, 2020, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original NDA submission for abrocitinib tablets, for oral use.

Labeling

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DDD on March 8, 2021 and are provided below.

Medication Guide: A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on March 1, 2021, and we have no comments.

Thank you for your consult. If you have any questions, please contact Laurie Buonaccorsi at (240) 402-6297 or laurie.buonaccorsi@fda.hhs.gov.

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/s/

LAURIE J BUONACCORSI
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Date of Consult Request: December 22, 2020 **Date**: February 16, 2021

From: Jean Limpert, MD, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Jane Liedtka, Acting Team Leader, Maternal Health
Division of Pediatric and Maternal Health

To: Division of Dermatology and Dentistry (DDD)

Drug: TRADENAME (abrocitinib)

NDA: 213871

Applicant: Pfizer, Inc.

Subject: Addendum to Consult Regarding Post-Marketing Requirements (PMRs)

Proposed Indication: TRADENAME is a Janus kinase (JAK) 1 inhibitor indicated for the treatment of (b) (4)

On December 22, 2020, DDD submitted a consult request to DPMH asking for input regarding PMRs for the above referenced NDA. See DPMH review for NDA 213871, TRADENAME (abrocitinib), Jean Limpert, MD, Medical Officer, January 14, 2021, DARRTs ID: 4735395 for full details.

After internal discussion with CDER's Office of Surveillance and Epidemiology (OSE) Office of Pharmacovigilance and Epidemiology (OPE) Division of Epidemiology (D-

EPI) 1, the PMR language for complementary studies for the above referenced NDA has been agreed upon.

The updated language for PMR for complementary studies does not include the term (b) (4) Removal of this term will allow for a broader response to complementary studies. (b) (4) This issue may be addressed at the protocol review phase.

The updated recommendations for PMR #2 is as follows:

> The applicant should be required to conduct an additional pregnancy study that uses a different design from the Pregnancy Exposure Registry (for example a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to abrocitinib during pregnancy compared to an unexposed control population.

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/s/

JEAN L LIMPERT
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JANE E LIEDTKA
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: January 14, 2021 **Date consulted:** December 22, 2020

From: Jean Limpert, MD, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Miriam Dinatale, DO, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Dermatology and Dentistry (DDD)

Drug: TRADENAME (abrocitinib)

NDA: 213871

Applicant: Pfizer, Inc.

Subject: Input for Postmarketing Requirements (PMRs)

Proposed Indication: TRADENAME is a Janus kinase (JAK) 1 inhibitor indicated for the treatment of (b) (4)

Materials Reviewed:

- DPMH consult request dated December 22, 2020, DARRTS reference ID 4721295
- Applicant's submitted background package and proposed labeling for NDA 213871, submitted August 25, 2020

- DPMH review for [redacted] (tralokinumab), BLA 761180, December 1, 2020, Jean Limpert, MD, Medical Officer, DARRTs reference ID: 4715000[1]
- DPMH labeling review for Dupixent, BLA 761055, January 13, 2017, Christos Mastroyannis, MD, Medical Officer, DARRTs reference ID: 4041992[2]

Consult Question: "DDD is in review of abrocitinib (JAK inhibitor) for the treatment of atopic dermatitis. During review, DDD noticed discrepancies in the requirement for pregnancy registries. Specifically, tofacitinib, tralokinumab, and dupilumab has a pregnancy registry, but upadacitinib does not. Please provide clarification as to when a pregnancy registry is required for these products and whether DPMH would suggest a pregnancy registry for abrocitinib (NDA 213871)."

INTRODUCTION AND BACKGROUND

On August 25, 2020, Pfizer Inc. submitted an original new drug application (NDA) for abrocitinib, a new molecular entity. The proposed indication is the treatment of moderate-severe AD. [redacted] On December 22, 2020, DDD consulted DPMH to provide input as to whether pregnancy postmarketing requirements (PMRs) are recommended.

Regulatory History

- Abrocitinib is an oral JAK1 inhibitor. The JAK pathway is involved in cell adhesion and cell polarity which can affect early embryonic development. Animal data for the class of JAK inhibitors indicates varying degrees of embryofetal toxicity including embryofetal toxicity warnings for some drugs in the class (e.g., upadacitinib).
- There are no JAK inhibitors approved for the treatment of moderate-severe AD but there are JAK inhibitors currently under review by DDD for this indication.
    - In July 2020, DDD consulted DPMH for Olumiant (baricitinib), a JAK inhibitor with a proposed indication of moderate-severe AD. The DPMH consult for Olumiant is currently pending. [redacted]
- Dupilumab is the first and only systemic biologic product currently approved for the treatment for moderate-severe AD. Dupilumab is a human monoclonal IgG4 antibody. In 2016, DDD (formerly the Division of Dermatology and Dental Products) consulted DPMH for pregnancy and lactation labeling. [3] DPMH recommended PMRs for a pregnancy exposure registry and complementary study and these PMRs were issued at the time of approval in March 2017.

[1] The [redacted] review was part of the materials reviewed but was not a source relied upon for the labeling recommendations in this consult review.
[2] The Dupixent review was part of the materials reviewed but was not a source relied upon for the labeling recommendations in this consult review.
[3] DPMH labeling review for Dupixent, BLA 761055, January 13, 2017, Christos Mastroyannis, MD, Medical Officer, DARRTs reference ID: 4041992

- In October 2020, DDD consulted DPMH for (b) (4) (tralokinumab), a fully human immunoglobulin G subclass (IgG4) monoclonal antibody to IL-13 with a proposed indication of moderate-severe AD. DPMH recommended PMRs including a pregnancy exposure registry, complementary study, and lactation study.[4] (b) (4) is still under review by DDD.
- There are three JAK inhibitors approved for the treatment of moderate-severe rheumatoid arthritis (Olumiant (baricitinib) NDA 207924, Xeljanz (tofacitinib) NDA 203214, and Rinvoq (upadacitinib) NDA 211675).
    - These drugs were initially reviewed by the Division of Rheumatology and Transplant medicine (formerly the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)). Postmarketing requirements were not issued for these products. There is a disease-based pregnancy registry for autoimmune diseases established by the Organization of Teratology Information Specialists (OTIS). The Sponsor for tofacitinib has a Pregnancy Exposure Registry conducted by OTIS within the existing OTIS Autoimmune Diseases registry.

Drug Characteristics[5,6]

- JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellar processes of hematopoiesis and immune cell function. Within the signaling pathway, JAKs phosphorylate and activate Signal Transducers and Activators of Transcription (STATs) which modulate intracellular activity including gene expression. Abrocitinib modulates the signaling pathway at the point of JAK1, preventing phosphorylation and activation of STATs.
- Proposed dosing: 100 mg orally once daily
- Bioavailability: 64%, protein binding of active metabolites M1 and M2 are 37% and 29%
- Mean elimination half-life of abrocitinib and its two active metabolites: 3-5 hours
- Molecular weight: 323.4 Daltons
- Adverse reactions from clinical trials: nausea, headache, acne, herpes simplex, vomiting, dizziness, and increase in blood creatinine phosphokinase
- Based on adverse reactions observed in clinical trials, there is a potential risk of serious infections, malignancy, retinal detachment, and thrombosis

Reviewer comment: This reviewer confirmed the accuracy of the drug characteristics with the review team.[7]

REVIEW
PREGNANCY
AD and Pregnancy

[4] DPMH consult for (b) (4) (tralokinumab), BLA 761180, December 1, 2020, Jean Limpert, MD, Medical Officer, DARRTs reference ID: 4715000.
[5] Applicant's submission, clinical overview, August 2020
[6] Applicant's proposed labeling, August 2020
[7] E-mail correspondence from 1/22/21

It is estimated up to 10% of adults in the United States are affected by AD though prevalence estimates are limited and vary based on case definitions.[8] For adults with AD, an estimated 44-57% have moderate disease and 12-21% have severe disease. Approximately half of the AD population are females and AD affects all age groups including women of reproductive potential.[9] AD does not have negative effects on fertility.[10]

Initial therapies include topical treatments and phototherapy. Systemic therapies are recommended when AD is not adequately controlled by these initial therapies and are typically needed for patients with moderate-severe AD. There are no JAK inhibitors currently approved for AD. There are currently two approved systemic therapies for patients with moderate-severe AD (i.e., systemic corticosteroids and dupilumab). Systemic corticosteroids can be effective for severe acute exacerbations but are not recommended for long-term use. Use of systemic corticosteroids during pregnancy may result in adverse effects including elevated blood pressure, glucose intolerance, susceptibility to infection, and fetal growth restriction. Dupilumab is an injectable systemic IgG4 monoclonal antibody. Current data in pregnancy are limited to one case report and limited cases in clinical trials, but there are no known safety issues for use during pregnancy. [11,12,13]

Nonclinical Experience

In embryo-fetal development studies, oral administration of abrocitinib to pregnant rabbits and rats resulted in increased embryo-fetal lethality (rats only) and skeletal abnormalities at exposures 4 and 17 times the maximum recommended human dose (MRHD) respectively. In rats, skeletal effects were also seen at exposures of 11 times the MRHD but without evidence of embryo-fetal lethality.

In a rat pre- and postnatal development study, oral administration of abrocitinib resulted in dystocia with prolonged parturition, lower offspring body weight, and lower postnatal survival at exposures greater than or equal to 11 times the MRHD. No maternal or developmental toxicity was noted at exposures 2.4 times the MRHD.

The reader is referred to the full Pharmacology/Toxicology review (currently pending) by John Dougherty, PhD.

Review of Human Pregnancy Data

The applicant conducted six studies in the AD clinical development program (n=2,856).

[8] Chiesa Fuxench ZC, Block JK, Boguniewicz M, et al. Atopic Dermatitis in America Study: a cross-sectional study examining the prevalence and disease burden of atopic dermatitis in the US adult population. *J Invest Dermatol.* 2019;139(3):583-590.

[9] Heilskov, S., Deleuran, M.S. & Vestergaard, C. Immunosuppressive and Immunomodulating Therapy for Atopic Dermatitis in Pregnancy: An Appraisal of the Literature. *Dermatol Ther (Heidelb)* **10,** 1215–1228 (2020).

[10] Langan, S.M.; Irvine, A.D.; Weidinger, S. Atopic dermatitis. Lancet 2020, 396, 345–360.

[11] Kage P, Simon JC, Treudler R. A case of atopic eczema treated safely with dupilumab during pregnancy and lactation. J Eur Acad Dermatol Venereol. 2020:34(6):e256–7.

[12] Heilskov, S., Deleuran, M.S. & Vestergaard, C. Immunosuppressive and Immunomodulating Therapy for Atopic Dermatitis in Pregnancy: An Appraisal of the Literature. *Dermatol Ther (Heidelb)* **10,** 1215–1228 (2020).

[13] DPMH labeling review for Dupixent, BLA 761055, January 13, 2017, Christos Mastroyannis, MD, Medical Officer, DARRTs reference ID: 4041992

As of April 22, 2020, there have been ten cases of pregnancies reported in subjects exposed to abrocitinib in the AD clinical program.[14] Of these, there were seven maternal exposures and three paternal exposures. For the maternal exposures, two cases resulted in miscarriage and five cases had unknown outcomes. For the paternal exposures, one outcome was a full-term live birth and two cases had unknown outcomes.

Reviewer comment: While the sponsor provided pregnancy outcome information for paternal exposures, these data do not inform the risk of exposure of abrocitinib during pregnancy. Additionally, there are no concerns for genotoxicity that would make the results from paternal exposures relevant.

DISCUSSION AND CONCLUSIONS

Pregnancy

AD is a common disease that affects up to 10% of adults and of those affected, it is likely more than half of these adults have moderate-severe disease for which systemic immunomodulators may be needed, including in females of reproductive potential.

There are currently no published data on abrocitinib use in pregnancy. In clinical trials, pregnant women were excluded, and females of reproductive potential were expected to use effective contraception. Pregnancy outcome data from clinical trials includes seven maternal exposures, including two miscarriages and five unknown outcomes. The applicant also reported three paternal exposures from clinical trials; there are no concerns for genotoxicity; therefore, the results from paternal exposure are not relevant. Pregnancy outcome information was not consistently collected for women who became pregnant in the clinical trials and the available human data are not adequate to assess the safety of abrocitinib use in pregnancy.

Given the anticipated use of abrocitinib in females of reproductive potential who may become pregnant, and the limited information collected in the clinical trials to date, post-marketing studies should be considered . Furthermore, pregnancy outcome information was not collected in the 5 out of 7 female patients who became pregnant after exposure. There is currently not a disease-based registry for atopic dermatitis. DPMH recommends a pregnancy registry study and a complementary study. Although the pregnancy registry will be an important tool for the collection of safety data in pregnant women exposed to abrocitinib due to its prospective design and ability to collected detailed patient information, based on experience with other pregnancy registries, we anticipate it will take several years for a pregnancy registry to provide adequate information and may not be sufficient by itself to assess the safety of abrocitinib during pregnancy. Therefore, a complementary study may provide additional understanding regarding safety in pregnancy and may address limitations inherent to a pregnancy registry providing greater confidence in the pregnancy outcomes that are observed. For more information, see the May 2019 FDA draft Guidance for Industry Postapproval Pregnancy Safety Studies.[15]

[14] Applicant's Summary of Clinical Safety, pages 220-221

[15] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postapproval-pregnancy-safety-studies-guidance-industry

Lactation

There are no available clinical data regarding the presence of abrocitinib in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. Abrocitinib is transferred into the milk of lactating rats. Given that abrocitinib will be used in females of reproductive potential with atopic dermatitis and based on the lack of available data in lactating women, DPMH recommends a PMR for a clinical lactation study. DPMH notes proposed labeling includes a statement that lactation is not recommended, likely due to the risks of serious adverse events seen in adult patients taking abrocitinib (e.g., serious infections, malignancy, and thrombosis). Thus, women who are taking the drug as prescribed and who wish to continue breastfeeding should not be enrolled in a lactation study because exposure of the drug to their infants would pose a potential risk. Therefore, DPMH recommends that a milk only study that enrolls only healthy volunteers or breastfeeding women prescribed abrocitinib who are willing to discontinue breastfeeding. For more information, see the May 2019 FDA draft Guidance for Industry Clinical Lactation Studies: Considerations for Study Design.[16]

DPMH RECOMMENDATIONS FOR POSTMARKETING REQUIREMENTS (PMR)

DPMH recommends the following:

1. The applicant should be required to conduct a Pregnancy Exposure Registry, a prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to abrocitinib during pregnancy to an unexposed control population. The registry should be designed to detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life. For more information, see the May 2019 FDA draft Guidance for Industry Postapproval Pregnancy Safety Studies. [17]
2. The applicant should be required to conduct an additional pregnancy study that uses a different design from the Pregnancy Exposure Registry (for example a retrospective cohort study using claims or electronic medical record data with outcome validation or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to abrocitinib during pregnancy compared to an unexposed control population.
3. The applicant should be required to conduct a lactation study (milk only) in healthy lactating women who volunteer for clinical research and/or women prescribed abrocitinib who are willing to discontinue breastfeeding their infants. A milk-only study is recommended because of the risk of serious adverse events seen in adult patients who have taken abrocitinib. In this type of study, the infant is not exposed to abrocitinib. For more information, see the May 2019 FDA draft Guidance for Industry Clinical Lacton Studies: Considerations for Study Design.[18]

[16] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-lactation-studies-considerations-study-design

[17] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postapproval-pregnancy-safety-studies-guidance-industry

[18] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-lactation-studies-considerations-study-design

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/s/

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MIRIAM C DINATALE
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LYNNE P YAO
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Medical Officer's Review of NDA 213871
Ophthalmology Consultant #2
Including updated information from January 11, 2021

NDA 213871

Submissions: 8/25/2020
1/11/2021
Review completed: 1/25/2021

Name: Abrocitinib tablets

Sponsor: Pfizer, Inc

Pharmacologic Category: Janus kinase (JAK) inhibitor

Indications: Atopic dermatitis (AD)

Requested: Pfizer is developing a Janus Kinase inhibitor (abrocitinib) for the treatment of moderate-to-severe atopic dermatitis (b) (4) During the clinical trials, there were two retinal detachment cases. DDD is asking for an ophthalmology consult for the Division's opinions on the relationship of JAK inhibitors and retinal detachment.

Subject ID: B7451012 (b) (6) PF-04965842 Protocol B7451012
This subject was enrolled in a Phase 3 randomized, double-blind, placebo-controlled, parallel group, multi-center study to evaluate the efficacy and safety of PF-04965842 monotherapy in subjects with moderate to severe atopic dermatitis (B7451012). A serious adverse event of retinal detachment on (b) (6) (Study Day 64) that ended on (b) (6) (Study Day 106) leading to permanent discontinuation from study treatment.

Demographics

Randomization Date	Age at Study Start	Sex	Race	Country	Weight	Height
(b) (6)	17 years	Female	White	United States	60.5 kilograms	156 centimeters

MedDRA Preferred Term	Start Date	End Date
Atrial septal defect	(b) (6)	Ongoing
Dermatitis atopic		Ongoing
Drug hypersensitivity		Ongoing
Asthma		Ongoing
Conjunctivitis allergic		Ongoing
Food allergy		Ongoing
Milk allergy		Ongoing
Seasonal allergy		Ongoing
Attention deficit/hyperactivity disorder		Ongoing
Menstruation irregular		Ongoing
Impetigo		(b) (6)

Study Treatment

Treatment	Dose	Route	Start Day	End Day
PF-04965842	100 mg QD	Oral	(b) (6) (Study Day 1)	(b) (6) (Study Day 63)

Serious Adverse Event

The subject experienced a serious adverse event of retinal detachment on (b) (6) (Study Day 64).

MedDRA Preferred Term: Retinal detachment	**Investigator Term:** Bilateral retinal detachment
Seriousness: Yes	**Case Number:** 2018289842
Start Day: Study Day 64	**End Day:** Study Day 106
Toxicity Grade/Severity: Severe	**Most Recent Dose administered on:** (b) (6) (Study Day 63)
	Outcome: Recovered/Resolved
Led to Permanent Discontinuation from Study (Yes/No): No	**Led to Permanent Discontinuation from Study Treatment (Yes/No):** Yes
Date of Discontinuation from Study: (b) (6) (Study Day 79)	**Date of Death:** Not applicable
Concomitant Treatment or Additional Treatment Given (Yes/No): Yes	**Adjudication Event ID:** Not applicable

Narrative Summary

This was a 17-year-old White female subject in the United States with a history of atopic dermatitis (since (b) (6)). The subject received PF-04965842 100 mg from (b) (6) (Study Day 1) to (b) (6) (Study Day 63).

Past medical history included impetigo (from (b) (6) to (b) (6)). Current medical history included atrial septal defect (since (b) (6)); drug hypersensitivity:rocephin (since (b) (6)); asthma (since (b) (6)); conjunctivitis allergic, food allergy and seasonal allergy (since (b) (6)); attention deficit/hyperactivity disorder (since (b) (6)); and irregular menstruation (since (b) (6)). Prior medications taken for atopic dermatitis included topical triamcinolone (from (b) (6) to (b) (6)), topical crisaborole (from (b) (6) to (b) (6) (b) (6)), and oral prednisolone (from (b) (6) to (b) (6)). Concomitant medications included oral methylphenidate hydrochloride (since (b) (6)) for attention deficit hyperactivity disorder, oral cetirizine (since (b) (6)) for seasonal allergic rhinitis, salbutamol sulfate (respiratory inhalation, since (b) (6)) for mild intermittent asthma, ophthalmic olopatadine hydrochloride (since (b) (6)) for seasonal allergic rhinitis, salbutamol (respiratory inhalation, since (b) (6)) for mild intermittent asthma, oral montelukast and nasal mometasone furoate (since (b) (6) (b) (6)) for seasonal allergic rhinitis, and oral drospirenone/ethinylestradiol (since (b) (6)) for birth control.

On an unknown date, the subject had initial symptoms of loss of vision (right eye more than left), flashes, floaters (right eye), and blurry milk vision. On (b) (6) (Study Day 63), the subject had ophthalmological examination which revealed bilateral cataract, bilateral amblyopia, left eye hypermetropia, left hyperopic astigmatism with no improvement. The subject was referred to pediatric ophthalmologist on (b) (6) (Study Day 64). On the same day (Study Day 64), the ophthalmological examination noted bilateral vitreous degeneration, bilateral retinal detachments

(retinal detachment with proliferative vitreoretinopathy of left eye and retinal detachment with single break of right eye), and intertemporal retinal dialysis with localized subretinal fluid/proliferative vitreoretinopathy. A serious adverse event of retinal detachment was reported on (b) (6) (Study Day 64). The Investigator considered the event of retinal detachment to be severe and medically significant. The study drug was permanently discontinued in response to the event of retinal detachment with the last dose taken on (b) (6) (Study Day 63). The subject underwent cryotherapy and scleral buckle procedure for the left eye on (b) (6) (Study Day 67). On the same day (Study Day 67), the subject was diagnosed with bilateral cataracts. The Investigator considered the event of cataract to be moderate in severity.

Additionally on (b) (6) (Study Day 53), the subject experienced an adverse event of left eyebrow folliculitis. The Investigator considered the event of folliculitis to be moderate in severity. No treatment was reported for the event. The event of left eyebrow folliculitis resolved on (b) (6) (Study Day 69). The subject was discontinued from the study on (b) (6) (Study Day 79), as she no longer wanted to participate in the trial.

The subject underwent left eye cataract surgery on (b) (6) (Study Day 80), and cryotherapy and scleral buckle procedure for the right eye on (b) (6) (Study Day 106). She was administered with dexamethasone/neomycin/polymyxin B and atropine sulfate 1% drops for the right eye (unknown dates). The events of bilateral cataract and retinal detachment were considered resolved on (b) (6) (Study Day 106).

In the opinion of the Investigator, the event of retinal detachment was not related to the study drug, concomitant medications, or a clinical trial procedure; but was due to "other - ocular trauma secondary to pruritus." The study Sponsor concurred with the Investigator and did not attribute the event to the study drug, concomitant medications, or a clinical trial procedure. This narrative reflects information available to the Sponsor as of 30 Apr 2019.

Concomitant medications reported within 14 days before the onset of the event and through the end of study

Treatment	Start Day	End Day
Ritalin	Study Day -3635	Ongoing
Ritalin la	Study Day -3635	Ongoing
Cetirizine	Study Day -2905	Ongoing
Proair – albuterol	Study Day -2691	Ongoing
Proventil	Study Day -1595	Ongoing
Pataday eyedrops	Study Day -1595	Ongoing
Montelukast	Study Day -1536	Ongoing
Nasonex	Study Day -1536	Ongoing
Yasmin	Study Day -27	Ongoing

Concomitant non-drug treatment/surgeries were reported within 14 days before the onset of the event and through the end of study

Treatment	Start Day	End Day
Cryotherapy left eye	Study Day 67	Study Day 67
Scleral buckle procedure left eye	Study Day 67	Study Day 67

Other Non-Serious Adverse Events

MedDRA Preferred Term/Investigator Term	Toxicity Grade or Severity	Start Day	End Day
Folliculitis/Left eyebrow folliculitis	Moderate	Study Day 53	Study Day 69
Cataract/Bilateral cataract	Moderate	Study Day 67	Study Day 106

Reviewer's Comments: *Temporal retinal dialysis associated with eye rubbing in an individual with facial atopic dermatitis and severe allergic conjunctivitis. It is more likely that severe eye rubbing was the cause of the bilateral retinal detachments than the drug product.*

Subject ID: B7451014 (b) (6)

Subject originally enrolled in B7451014 study and treated received open-label treatment with PF-04965842 200 mg once daily (QD) for 92 days. The subject was subsequently enrolled in B7451015, a Phase 3 multi-center, long-term extension study investigating the efficacy and safety of PF-04965842 for severe atopic dermatitis. This narrative summarizes all relevant subject participation available through to the 22 Apr 2020 database snapshot.

Demographics:

Randomization Date	Age at B7451014 Study Start	Age at B7451015 Study Start	Sex	Race	Country	Weight	Height
(b) (6)	19 years	19 years	Male	White	Poland	66 kilograms	185 centimeters

Relevant Medical History:

MedDRA Preferred Term	Start Date	End Date
Dermatitis atopic#	(b) (4)	Not Available
Conjunctivitis allergic		Ongoing
Rhinitis allergic		Ongoing
Cataract		(b) (6)

This is a primary diagnosis event. If there is no End Date, "Not Available" will be displayed.

Medications Used Prior to the B7451014 Study for Atopic Dermatitis:

Treatment	Start Day	End Day
Latopic	B7451014 Study Day -1124	Ongoing
Methylprednisolone acetonate	B7451014 Study Day -100	B7451014 Study Day -55

Study Treatments

Study	Assigned Treatment	Start Dose Frequency Route of Administration	Start Date	End Date
B7451014	PF-04965842 (Open-Label)	200 mg QD Oral	(b) (6) (B7451014 Study Day 1)	(b) (6) (B7451014 Study Day 92)
B7451015	PF-04965842	200 mg QD Oral	(b) (6) (B7451015 Study Day 1)	Ongoing

Serious Adverse Event:

The subject also experienced serious dermatitis atopic on [redacted] (B7451015 Study Day 169).

MedDRA Preferred Term: Dermatitis atopic	**Investigator Term:** Acceleration of atopic dermatitis
Seriousness: Yes	**Case Number:** 2019453088
Start Day: B7451015 Study Day 169	**End Day:** B7451015 Study Day 171
Toxicity Grade/Severity: Severe	**Most Recent Dosing Date Prior to the Onset of the AE:** [redacted] (B7451015 Study Day 169)
	Outcome: Recovered/Resolved
Led to Permanent Discontinuation from Study (Yes/No): No	**Led to Permanent Discontinuation from Study Treatment (Yes/No):** No

Narrative Summary:

This subject was a 19-year-old White male in Poland who had a history of atopic dermatitis (since [redacted]). The subject entered Study B7451014 and received treatment with open-label PF-04965842 200 mg QD from [redacted] to [redacted] (B7451014 Study Day 1 to 92). During the course of participation in B7451014 Study, the subject experienced a serious adverse event of retinal detachment. On [redacted] (B7451014 Study Day 85), the subject was diagnosed with a serious adverse event of retinal detachment of the left eye, resulting in hospitalization on the same day. The Investigator considered the event to be severe in severity. The subject received levofloxacin (Oftaquix) and dexamethasone sodium phosphate (Dexafree) from [redacted] to [redacted] (B7451014 Study Day 87 to 92) for retinal detachment. The study drug was temporarily interrupted in response to the event of retinal detachment with the most recent dose administered on [redacted] (B7451014 Study Day 85). On [redacted] (B7451014 Study Day 86), the subject underwent ophthalmic surgery. On [redacted] (B7451014 Study Day 87), the study drug was resumed, and the event of retinal detachment resolved on the same day. The subject was discharged from the hospital on an unknown date. In the opinion of the Investigator, the event of retinal detachment was considered unrelated to the study drug, concomitant medications, or a clinical trial procedure; however, this serious adverse event was probably related to cataract surgery on [redacted] The study Sponsor concurred with the Investigator's causality assessment. On [redacted] (B7451014 Study Day 92), the subject completed treatment in the open- label run-in period in the B7451014 Study. On [redacted] (B7451015 Study Day 1), the subject was allocated to PF-04965842 200 mg QD and started receiving treatment in this B7451015 Extension Study. This narrative reflects information available to the Sponsor as of 18 May 2020.

Concomitant medications reported within 14 days before the onset of the event and through the end of the study.

Treatment	Start Day	End Day
Latopic	B7451015 Study Day -1216	Ongoing
Alphagan (brimonidine tartrate)	B7451015 Study Day 1	Ongoing
Aspargin magnesium hydroaspartate/potassium hydroaspartate	B7451015 Study Day 1	Ongoing
Cosopt	B7451015 Study Day 1	Ongoing
Diuramid	B7451015 Study Day 1	Ongoing
Xalatan (latanoprost)	B7451015 Study Day 21	Ongoing
Amertil	B7451015 Study Day 28	Ongoing
Clemastin	B7451015 Study Day 28	Ongoing
Elocom	B7451015 Study Day 28	Ongoing

The subject also experienced the following non-serious adverse event during the course of the study.

MedDRA Preferred Term/Investigator Term	Toxicity Grade or Severity	Start Day	End Day
Skin bacterial infection/Bacterial superinfection of skin lesions	Mild	B7451014 Study Day 13	B7451014 Study Day 23
Intraocular pressure increased/High eye pressure	Mild	B7451015 Study Day 55	Ongoing

Supplemental Information provided on January 11, 2021
There were cataracts in both eyes and surgery was done for both eyes in (b) (6) The retinal detachment was not of rhegmatogenous origin.

Reviewer's Comments: *Previous cataract surgery is a known risk factor for developing a retinal detachment.*

Subject ID: **B7451013** (b) (6)
B7451015 (b) (6)

This subject was a 62-year-old White female in Poland who had a history of atopic dermatitis (since (b) (6)). The subject was randomized in Study B7451013 and received treatment with PF-04965842 100 mg QD, from (b) (6) (B7451013 Study Day 1) to (b) (6) (B7451013 Study Day 88). The subject completed treatment in the B7451013 Study and was allocated to PF-04965842 100 mg QD in a blinded manner and started receiving treatment in this B7451015 Extension Study on (b) (6) (B7451015 Study Day 1). Past and current medical history included atopic dermatitis.

On (b) (6) (B7451015 Study Day 242, Exposure Day 330 relative to start of B7451013), the subject experienced a non-serious event of retinal detachment. The Investigator considered the event to be moderate in severity. No treatment was reported for the event of retinal detachment and no action was taken with the study drug in response to the event. The event was considered resolved on the same day on (b) (6) (B7451015 Study Day 242).

Reviewer's Comments: *As noted below, the subject was treated for a rhegmatogenous retinal detachment.*

Six weeks before the reported retinal detachment, the patient underwent a cataract surgery of the right and left eye by phacoemulsification on (b) (6) performed in the Czech Republic and reimbursed by the Polish National Health Fund. The cataract diagnosis took place approximately 3 weeks before the operation. On (b) (6) due to retinal detachment, the patient underwent cryotherapy treatment of the retinal detachment (procedure performed in Poland). The investigator indicated this should be AE grade 2, right and left cataracts starting on (b) (6) (The patient did not report any complaints indicating cataracts) and ending (b) (6) The investigator considers this not related to IP and not related to audit procedures B7451015.

The subject's baseline Day 1 IGA score was 3, EASI sub-score for head/neck was 3, SCORAD Area of Involvement for Head/Neck was 3. and PP-NRS was 6. On (b) (6) (B7451015

Study Day 252, Exposure Day 340) was 0, EASI sub-score for head/neck was 0, and PP-NRS was 0.

Reviewer's Comments: *Cryotherapy is used to treat retinal detachments which have breaks in the retina (rhegmatogenous), often in the anterior portion of the retina. These types of breaks in patients with atopic dermatitis of the face are often due to severe eye rubbing.*

Randomization Date	Age at B7451013 Study Start	Age at B7451015 Study Start	Sex	Race	Country	Weight	Height
(b) (6)	61 Years	62 Years	Female	White	POL	71 kgms	160 cm

Details of the adverse event are listed below:

MedDRA Preferred Term: Retinal detachment	Investigator Term: PARTIAL RETINAL DETACHMENT
Seriousness: N	Case Number: Not Available
Start Date (Day): (b) (6) (B7451015 Study Day 242)	End Date (Day): (b) (6) (B7451015 Study Day 242)
Toxicity Grade / Severity: MODERATE	Most Recent Dosing Date Prior to the Onset of the AE: (b) (6) (b) (6) (B7451015 Study Day 242)
	Outcome: RECOVERED/RESOLVED
Led to Permanent Discontinuation from Study (Yes/No): No	Led to Permanent Discontinuation from Study Treatment (Yes/No): No
Date of Discontinuation from Study: NA	Date of Death: NA
Concomitant Treatment or Additional Treatment Given (Yes/No): N	Adjudication Event ID: NA

Reviewer's Comments: *The retinal detachment is more likely a result of severe eye rubbing that drug treatment.*

Summary Conclusions:
Three cases of retinal detachment have been reported. For two of the reports, it is more likely that severe eye rubbing was the cause of the retinal detachments than the drug product. For the third case, it is likely that the patient's previous cataract surgery was a major factor in the development of the retinal detachment. At this time, it is unlikely that the drug product is a significant cause of retinal detachments.

Wiley A. Chambers, M.D.
Supervisory Medical Officer, Ophthalmology

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/s/

WILEY A CHAMBERS
01/25/2021 08:35:42 AM

Medical Officer's Review of NDA 213871
Ophthalmology Consultant

NDA 213871 Submission: 8/25/2020
Review completed: 1/5/2021

Name: Abrocitinib tablets

Sponsor: Pfizer, Inc

Pharmacologic Category: Janus kinase (JAK) inhibitor

Indications: Atopic dermatitis (AD)

Requested: Pfizer is developing a Janus Kinase inhibitor (abrocitinib) for the treatment of moderate-to-severe atopic dermatitis (b) (4) During the clinical trials, there were two retinal detachment cases. DDD is asking for an ophthalmology consult for the Division's opinions on the relationship of JAK inhibitors and retinal detachment.

Subject ID: B7451012 (b) (6) PF-04965842 Protocol B7451012
This subject was enrolled in a Phase 3 randomized, double-blind, placebo-controlled, parallel group, multi-center study to evaluate the efficacy and safety of PF-04965842 monotherapy in subjects with moderate to severe atopic dermatitis (B7451012). A serious adverse event of retinal detachment on (b) (6) (Study Day 64) that ended on (b) (6) (Study Day 106) leading to permanent discontinuation from study treatment.

Demographics

Randomization Date	Age at Study Start	Sex	Race	Country	Weight	Height
(b) (6)	17 years	Female	White	United States	60.5 kilograms	156 centimeters

MedDRA Preferred Term	Start Date	End Date
Atrial septal defect	(b) (6)	Ongoing
Dermatitis atopic		Ongoing
Drug hypersensitivity		Ongoing
Asthma		Ongoing
Conjunctivitis allergic		Ongoing
Food allergy		Ongoing
Milk allergy		Ongoing
Seasonal allergy		Ongoing
Attention deficit/hyperactivity disorder		Ongoing
Menstruation irregular		Ongoing
Impetigo		(b) (6)

Study Treatment

Treatment	Dose	Route	Start Day	End Day
PF-04965842	100 mg QD	Oral	(b) (6) (Study Day 1)	(b) (6) (Study Day 63)

Serious Adverse Event

The subject experienced a serious adverse event of retinal detachment on (b) (6) (Study Day 64).

MedDRA Preferred Term: Retinal detachment	**Investigator Term:** Bilateral retinal detachment
Seriousness: Yes	**Case Number:** 2018289842
Start Day: Study Day 64	**End Day:** Study Day 106
Toxicity Grade/Severity: Severe	**Most Recent Dose administered on:** (b) (6) (Study Day 63)
	Outcome: Recovered/Resolved
Led to Permanent Discontinuation from Study (Yes/No): No	**Led to Permanent Discontinuation from Study Treatment (Yes/No):** Yes
Date of Discontinuation from Study: (b) (6) (Study Day 79)	**Date of Death:** Not applicable
Concomitant Treatment or Additional Treatment Given (Yes/No): Yes	**Adjudication Event ID:** Not applicable

Narrative Summary

This was a 17-year-old White female subject in the United States with a history of atopic dermatitis (since (b) (6)). The subject received PF-04965842 100 mg from (b) (6) (Study Day 1) to (b) (6) (Study Day 63).

Past medical history included impetigo (from (b) (6) to (b) (6)). Current medical history included atrial septal defect (since (b) (6)); drug hypersensitivity:rocephin (since (b) (6)); asthma (since (b) (6)); conjunctivitis allergic, food allergy and seasonal allergy (since (b) (6)); attention deficit/hyperactivity disorder (since (b) (6)); and irregular menstruation (since (b) (6)). Prior medications taken for atopic dermatitis included topical triamcinolone (from (b) (6) to (b) (6)), topical crisaborole (from (b) (6) to (b) (6) (b) (6)), and oral prednisolone (from (b) (6) to (b) (6)). Concomitant medications included oral methylphenidate hydrochloride (since (b) (6)) for attention deficit hyperactivity disorder, oral cetirizine (since (b) (6)) for seasonal allergic rhinitis, salbutamol sulfate (respiratory inhalation, since (b) (6)) for mild intermittent asthma, ophthalmic olopatadine hydrochloride (since (b) (6)) for seasonal allergic rhinitis, salbutamol (respiratory inhalation, since (b) (6)) for mild intermittent asthma, oral montelukast and nasal mometasone furoate (since (b) (6) (b) (6)) for seasonal allergic rhinitis, and oral drospirenone/ethinylestradiol (since (b) (6)) for birth control.

On an unknown date, the subject had initial symptoms of loss of vision (right eye more than left), flashes, floaters (right eye), and blurry milk vision. On (b) (6) (Study Day 63), the subject had ophthalmological examination which revealed bilateral cataract, bilateral amblyopia, left eye hypermetropia, left hyperopic astigmatism with no improvement. The subject was referred to pediatric ophthalmologist on (b) (6) (Study Day 64). On the same day (Study Day 64), the ophthalmological examination noted bilateral vitreous degeneration, bilateral retinal detachments

(retinal detachment with proliferative vitreoretinopathy of left eye and retinal detachment with single break of right eye), and intertemporal retinal dialysis with localized subretinal fluid/proliferative vitreoretinopathy. A serious adverse event of retinal detachment was reported on (b) (6) (Study Day 64). The Investigator considered the event of retinal detachment to be severe and medically significant. The study drug was permanently discontinued in response to the event of retinal detachment with the last dose taken on (b) (6) (Study Day 63). The subject underwent cryotherapy and scleral buckle procedure for the left eye on (b) (6) (Study Day 67). On the same day (Study Day 67), the subject was diagnosed with bilateral cataracts. The Investigator considered the event of cataract to be moderate in severity.

Additionally on (b) (6) (Study Day 53), the subject experienced an adverse event of left eyebrow folliculitis. The Investigator considered the event of folliculitis to be moderate in severity. No treatment was reported for the event. The event of left eyebrow folliculitis resolved on (b) (6) (Study Day 69). The subject was discontinued from the study on (b) (6) (Study Day 79), as she no longer wanted to participate in the trial.

The subject underwent left eye cataract surgery on (b) (6) (Study Day 80), and cryotherapy and scleral buckle procedure for the right eye on (b) (6) (Study Day 106). She was administered with dexamethasone/neomycin/polymyxin B and atropine sulfate 1% drops for the right eye (unknown dates). The events of bilateral cataract and retinal detachment were considered resolved on (b) (6) (Study Day 106).

In the opinion of the Investigator, the event of retinal detachment was not related to the study drug, concomitant medications, or a clinical trial procedure; but was due to "other - ocular trauma secondary to pruritus". The study Sponsor concurred with the Investigator and did not attribute the event to the study drug, concomitant medications, or a clinical trial procedure. This narrative reflects information available to the Sponsor as of 30 Apr 2019.

Concomitant medications reported within 14 days before the onset of the event and through the end of study

Treatment	Start Day	End Day
Ritalin	Study Day -3635	Ongoing
Ritalin la	Study Day -3635	Ongoing
Cetirizine	Study Day -2905	Ongoing
Proair – albuterol	Study Day -2691	Ongoing
Proventil	Study Day -1595	Ongoing
Pataday eyedrops	Study Day -1595	Ongoing
Montelukast	Study Day -1536	Ongoing
Nasonex	Study Day -1536	Ongoing
Yasmin	Study Day -27	Ongoing

Concomitant non-drug treatment/surgeries were reported within 14 days before the onset of the event and through the end of study

Treatment	Start Day	End Day
Cryotherapy left eye	Study Day 67	Study Day 67
Scleral buckle procedure left eye	Study Day 67	Study Day 67

Other Non-Serious Adverse Events

MedDRA Preferred Term/Investigator Term	Toxicity Grade or Severity	Start Day	End Day
Folliculitis/Left eyebrow folliculitis	Moderate	Study Day 53	Study Day 69
Cataract/Bilateral cataract	Moderate	Study Day 67	Study Day 106

Reviewer's Comments: *Temporal retinal dialysis associated with eye rubbing in an individual with facial atopic dermatitis and severe allergic conjunctivitis. It is more likely that severe eye rubbing was the cause of the bilateral retinal detachments than the drug product.*

Subject ID: B7451014 (b) (6)

Subject originally enrolled in B7451014 study and treated received open-label treatment with PF-04965842 200 mg once daily (QD) for 92 days. The subject was subsequently enrolled in B7451015, a Phase 3 multi-center, long-term extension study investigating the efficacy and safety of PF-04965842 for severe atopic dermatitis. This narrative summarizes all relevant subject participation available through to the 22 Apr 2020 database snapshot.

Demographics:

Randomization Date	Age at B7451014 Study Start	Age at B7451015 Study Start	Sex	Race	Country	Weight	Height
(b) (6)	19 years	19 years	Male	White	Poland	66 kilograms	185 centimeters

Relevant Medical History:

MedDRA Preferred Term	Start Date	End Date
Dermatitis atopic#	(b) (6)	Not Available
Conjunctivitis allergic		Ongoing
Rhinitis allergic		Ongoing
Cataract		(b) (6)

This is a primary diagnosis event. If there is no End Date, "Not Available" will be displayed.

Medications Used Prior to the B7451014 Study for Atopic Dermatitis:

Treatment	Start Day	End Day
Latopic	B7451014 Study Day -1124	Ongoing
Methylprednisolone aceponate	B7451014 Study Day -100	B7451014 Study Day -55

Study Treatments

Study	Assigned Treatment	Start Dose Frequency Route of Administration	Start Date	End Date
B7451014	PF-04965842 (Open-Label)	200 mg QD Oral	(b) (6) (B7451014 Study Day 1)	(b) (6) (B7451014 Study Day 92)
B7451015	PF-04965842	200 mg QD Oral	(b) (6) (B7451015 Study Day 1)	Ongoing

Serious Adverse Event:

The subject also experienced serious dermatitis atopic on (b) (6) (B7451015 Study Day 169).

MedDRA Preferred Term: Dermatitis atopic	**Investigator Term:** Acceleration of atopic dermatitis
Seriousness: Yes	**Case Number:** 2019453088
Start Day: B7451015 Study Day 169	**End Day:** B7451015 Study Day 171

Toxicity Grade/Severity: Severe	**Most Recent Dosing Date Prior to the Onset of the AE:** (b) (6) (B7451015 Study Day 169)
	Outcome: Recovered/Resolved
Led to Permanent Discontinuation from Study (Yes/No): No	**Led to Permanent Discontinuation from Study Treatment (Yes/No):** No

Narrative Summary:
This subject was a 19-year-old White male in Poland who had a history of atopic dermatitis (since (b) (6)). The subject entered Study B7451014 and received treatment with open-label PF-04965842 200 mg QD from (b) (6) to (b) (6) (B7451014 Study Day 1 to 92). During the course of participation in B7451014 Study, the subject experienced a serious adverse event of retinal detachment. On (b) (6) (B7451014 Study Day 85), the subject was diagnosed with a serious adverse event of retinal detachment of the left eye, resulting in hospitalization on the same day. The Investigator considered the event to be severe in severity. The subject received levofloxacin (Oftaquix) and dexamethasone sodium phosphate (Dexafree) from (b) (6) to (b) (6) (B7451014 Study Day 87 to 92) for retinal detachment. The study drug was temporarily interrupted in response to the event of retinal detachment with the most recent dose administered on (b) (6) (B7451014 Study Day 85). On (b) (6) (B7451014 Study Day 86), the subject underwent ophthalmic surgery. On (b) (6) (B7451014 Study Day 87), the study drug was resumed, and the event of retinal detachment resolved on the same day. The subject was discharged from the hospital on an unknown date. In the opinion of the Investigator, the event of retinal detachment was considered unrelated to the study drug, concomitant medications, or a clinical trial procedure; however, this serious adverse event was probably related to cataract surgery on (b) (6) The study Sponsor concurred with the Investigator's causality assessment. On (b) (6) (B7451014 Study Day 92), the subject completed treatment in the open- label run-in period in the B7451014 Study. On (b) (6) (b) (6) (B7451015 Study Day 1), the subject was allocated to PF-04965842 200 mg QD and started receiving treatment in this B7451015 Extension Study. This narrative reflects information available to the Sponsor as of 18 May 2020.

Concomitant medications reported within 14 days before the onset of the event and through the end of the study.

Treatment	Start Day	End Day
Latopic	B7451015 Study Day -1216	Ongoing
Alphagan (brimonidine tartrate)	B7451015 Study Day 1	Ongoing
Aspargin magnesium hydroaspartate/potassium hydroaspartate	B7451015 Study Day 1	Ongoing
Cosopt	B7451015 Study Day 1	Ongoing
Diuramid	B7451015 Study Day 1	Ongoing
Xalatan (latanoprost)	B7451015 Study Day 21	Ongoing
Amertil	B7451015 Study Day 28	Ongoing
Clemastin	B7451015 Study Day 28	Ongoing
Elocom	B7451015 Study Day 28	Ongoing

The subject also experienced the following non-serious adverse event during the course of the study.

MedDRA Preferred Term/Investigator Term	Toxicity Grade or Severity	Start Day	End Day
Skin bacterial infection/Bacterial superinfection of skin lesions	Mild	B7451014 Study Day 13	B7451014 Study Day 23
Intraocular pressure increased/High eye pressure	Mild	B7451015 Study Day 55	Ongoing

Reviewer's Comments: *There is insufficient information available to make an informed decision regarding the cause of the retina detachment. It would be important to know which eye(s) previously had a cataract and if the cataract(s) were removed. It would also be important to know if this was a rhegmatogenous retinal detachment and if so, where the break/tear was located.*

Summary Conclusions:

Two cases of retinal detachment have been reported. For one of the reports, it is more likely that severe eye rubbing was the cause of the bilateral retinal detachments than the drug product. For the second case, there is insufficient information to make an informed decision regarding the cause of the retina detachment. It would be important to know which eye(s) previously had a cataract and if the cataract(s) were removed. It would also be important to know if this was a rhegmatogenous retinal detachment and if so, where the break/tear was located.

Wiley A. Chambers, M.D.
Supervisory Medical Officer, Ophthalmology

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Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 213871
Submission Number	001
Submission Date	8/25/2020
Date Consult Received	10/7/2020
Drug Name	Abrocitinib
Indication	Moderate-To-Severe Atopic Dermatitis
Therapeutic dose	Up to 200 mg once daily
Clinical Division	DDD

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult dated 10/7/2020 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT review dated 06/07/2018 in DARRTS (link);
- Sponsor's clinical study protocol # B4751027 (SN0001; link);
- Sponsor's clinical study report # B4751027 (SN0001; link);
- Sponsor's proposed product label (SN0002; link);
- Investigator's brochure (SN0005; link); and
- Highlights of clinical pharmacology and cardiac safety (SN0005; link).

1 SUMMARY

No significant QTc prolongation effect of abrocitinib was detected in this QT assessment.

The effect of abrocitinib was evaluated in a thorough QT study (Study # B7451027). This was a phase-1, single-dose (600 mg), randomized, 3-treatment, 3-period crossover, placebo-and positive-controlled study in healthy subjects. The 600 mg dose covers the high clinical exposure scenario (CYP2C19 inhibition, section 3.1). The assay sensitivity was established using oral moxifloxacin.

The data were analyzed using exposure response analysis as the primary analysis, which did not suggest that abrocitinib is associated with significant QTc prolonging effect (refer to section 4.5) – see Table 1 for overall results.

Table 1: The Point Estimates and the 90% CIs (FDA Analysis)

ECG Parameter	Treatment	Concentration (ng/mL)	ΔΔQTcF (msec)	90% CI (msec)
QTc	Abrocitinib 600 mg	1891	5.3	3.9, 6.7

For further details on the FDA analysis, please see section 4.

The findings of this analysis are further supported by the available nonclinical data (sections 3.1.2) and by time analysis (section 4.3) and categorical analysis (section 4.4).

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

No QT labeling language was proposed by the sponsor in the label submitted to SN0002. Below is proposed text for Section 12.2 of the label from the IRT. Please note, that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics Cardiac Electrophysiology At a dose 1.5 times the maximum approved recommended dose, <Tradename> does not prolong the QT interval to any clinically relevant extent.
We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

Pfizer Inc. is developing abrocitinib for the treatment of moderate to severe atopic dermatitis. Abrocitinib (PF-04965842; MW: 323.42 Da) is a Janus kinase 1 inhibitor. The sponsor states that the administration of abrocitinib is associated with dose-dependent reduction in serum markers of inflammation, including high sensitivity C-reactive protein, interleukin-31, and thymus and activation regulated chemokine.

The product is formulated as an immediate-release film-coated tablet formulation containing 50, 100, 200 mg abrocitinib (free base) for oral administration. The maximum proposed therapeutic dose for the present indication is 200 mg once daily. The peak concentrations of 1184 ng/mL (Tmax: ~1 h; Half-life: ~5 h) are expected at steady-state with the anticipated therapeutic dose. No significant accumulation is expected at steady-state with the proposed maximum therapeutic dose (Racc: ~1.6). The maximum tolerated dose is not established, and the maximum studied dose is 800 mg as a single dose (Cmax: 3712 ng/mL in healthy subjects).

The studies indicate that abrocitinib is extensively metabolized by multiple enzymes including CYP2C19 (~53%), CYP2C9 (~30%), CYP3A4 (~11%) and CYP2B6 (~6%) forming as M1 (3 hydroxypropyl), M2 (2 hydroxypropyl), and M4 (pyrrolidinone pyrimidine) metabolites. Concomitant administration of abrocitinib with a strong inhibitor of CYP2C19 is expected to result in increased exposures of abrocitinib (Cmax: 1.84-fold & AUC: 2.75-fold). The sponsor proposes dose reduction (by ~50%) during concomitant administration of abrocitinib with the inhibitors of CYP2C19. Similar dose reduction is also suggested in subjects with moderate to severe renal impairment. In addition, the product is not intended to be administered concomitantly with strong CYP2C9 or CYP2C19 inducers (e.g., rifampin).

Previously, the IRT reviewed the sponsor's thorough QT study and the study design was found to be acceptable (Dt: 06/07/2018). This was a phase-1, single-dose (600 mg), randomized, 3-treatment, 3-period cross-over, placebo-and positive-controlled study in healthy subjects (n=36; Study # B7451027). Moxifloxacin administration was unblinded and the 3 treatment periods were separated by a washout period of at least 5 days. The peak concentration (Cmax: 1890 ng/mL) observed with highest dose studied (i.e., 600 mg single dose) is expected to offer only ~1.7-fold margin over the therapeutic exposures (Cmax: 1123 ng/mL; POP-PK) associated with the maximum proposed dose at the steady-state in target population.

3.1.2 Nonclinical Safety Pharmacology Assessments

Refer to the sponsor's highlights of clinical pharmacology and clinical safety and previous IRT review dated 06/07/2018 in DARRTS (link).

3.2 SPONSOR'S RESULTS

3.2.1 By Time Analysis

The primary analysis for abrocitinib was based on exposure response analysis, please see section 3.2.3 for additional details.

In by-time analysis, sponsor only provided descriptive statistics for ΔQTcF, ΔHR, ΔPR, and ΔQRS.

Reviewer's comment: *FDA reviewer used linear mixed models to analyze the drug effect for each biomarker. FDA reviewer's analysis results showed similar time trend as in sponsor's ΔQTcF by-time results.*

3.2.1.1 Assay Sensitivity

By-time analysis is the only analysis sponsor presented for assay sensitivity. In sponsor's report, by-time analysis for assay sensitivity shows that assay sensitivity was established by the moxifloxacin arm.

Reviewer's comment: *FDA reviewer's analysis also shows that assay sensitivity was established by the moxifloxacin arm.*

3.2.1.1.1 QT Bias Assessment

Not applicable.

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTc (i.e., > 500 msec or > 60 msec over baseline, HR (>100 beats/min), PR (>220 msec and 25% over baseline) and QRS (>120 msec and 25% over baseline).

Reviewer's comment: *FDA reviewer's analysis results are similar to the sponsor's results.*

3.2.3 Exposure-Response Analysis

The sponsor performed PK/PD analysis to explore the relationship between plasma concentration of abrocitinib and ΔQTcF (change from baseline in QTcF) using a linear mixed-effects approach on all subjects who had at least 1 pair of time-matched post-dose QT and plasma concentration values in at least 1 period of the study. The model predicted ΔΔQTcF (upper confidence interval) values of 3.87 (4.84) msec at the mean peak concentrations for the therapeutic exposures (AD patients) following oral administration. The results of the sponsor's analysis suggest an absence of significant QTc prolongation at the highest studied dose.

Reviewer's comment: Although there are numerical differences, the results of the reviewer's analysis agreed with the sponsor's conclusion. Please see Section 4.5 for additional details.

3.2.4 Safety Analysis

No deaths, SAEs, discontinuations from the study or study treatment due to AEs, temporary discontinuations or dose reductions due to AEs and medication errors were reported during the study.

More TEAEs were reported on the PF-04965842 600 mg treatment compared to moxifloxacin 400 mg and placebo treatments. This difference was primarily driven by more frequent AEs of nausea, diarrhea and headache during the PF-04965842 600 mg treatment.

There were no clinically significant findings noted for physical examinations, vital signs values and ECG data.

Reviewer's comment: None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis, which is acceptable as no large increases or decreases in heart rate (i.e. |mean| < 10 beats/min) were observed (see Section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Overall ECG acquisition and interpretation in this study appears acceptable.

4.2.2 QT Bias Assessment

Not applicable.

4.3 By Time Analysis

The analysis population used for by time analysis included all subjects with a baseline and at least one post-dose ECG.

The statistical reviewer used linear mixed model to analyze the drug effect by time for each biomarker (e.g., ΔQTcF, ΔHR) independently. The default model includes treatment, sequence, period, time (as a categorical variable), and treatment-by-time interaction as fixed effects and baseline as a covariate. The default model also includes subject as a random effect and an unstructured covariance matrix to explain the associated between repeated measures within period.

4.3.1 QTc

Figure 1 displays the time profile of ΔΔQTcF for different treatment groups. The maximum ΔΔQTcF values by treatment are shown in Table 2.

Figure 1: Mean and 90% CI of ΔΔQTcF Timecourse (unadjusted CIs).

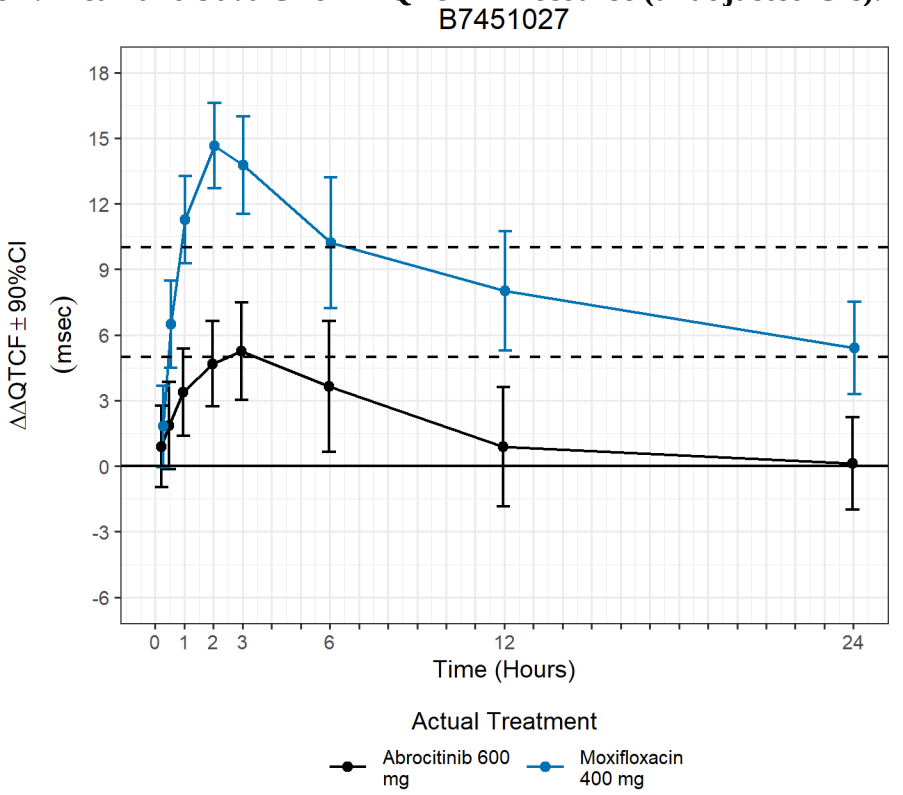


Table 2: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔΔQTcF

Actual Treatment	Nact / Npbo	Time (Hours)	ΔΔQTCF (msec)	90.0% CI (msec)
Abrocitinib 600 mg	36 / 36	3.0	5.3	(3.0 to 7.5)

4.3.1.1 Assay sensitivity

The statistical reviewer used the same linear mixed model for the assay sensitivity. The time-course of changes in ΔΔQTcF is shown in Figure 1 and shows the expected time-profile with a mean effect of > 5 msec after Bonferroni adjustment for 4 time points (Table 3).

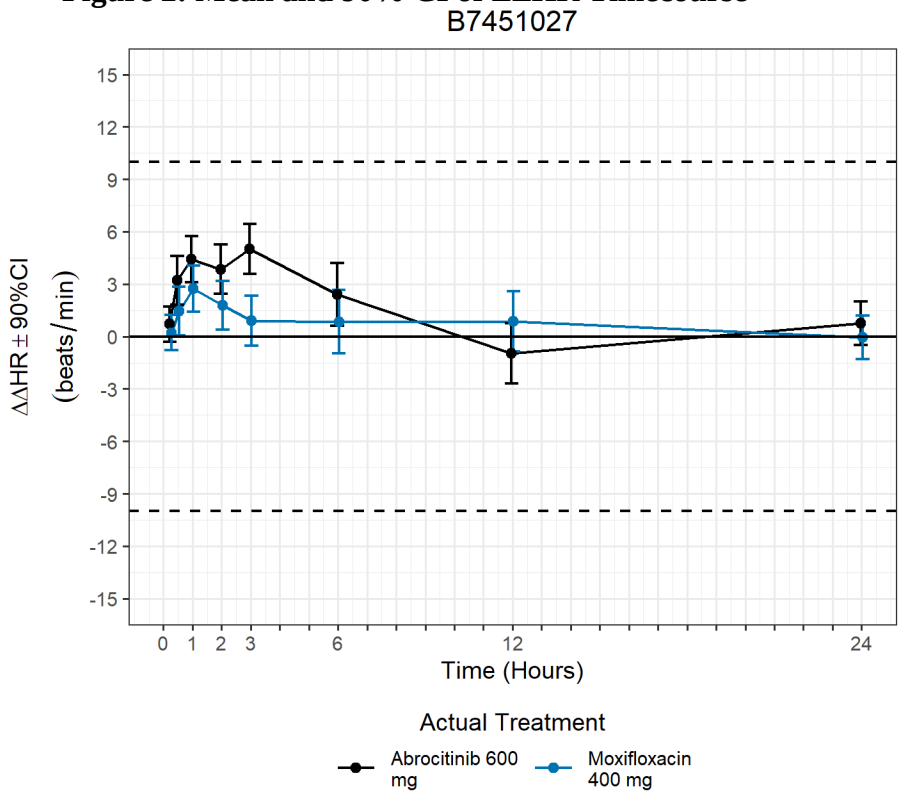
Table 3: The Point Estimates and the 90% CIs Corresponding to the Largest Lower Bounds for ΔΔQTcF

Actual Treatment	N	Time (hours)	ΔΔQTCF (msec)	90.0% CI (msec)	97.5% CI (msec)
Moxifloxacin 400 mg	36	2.0	14.6	12.7, 16.6	12.0, 17.3

4.3.2 HR

Figure 2 displays the time profile of ΔΔHR for different treatment groups.

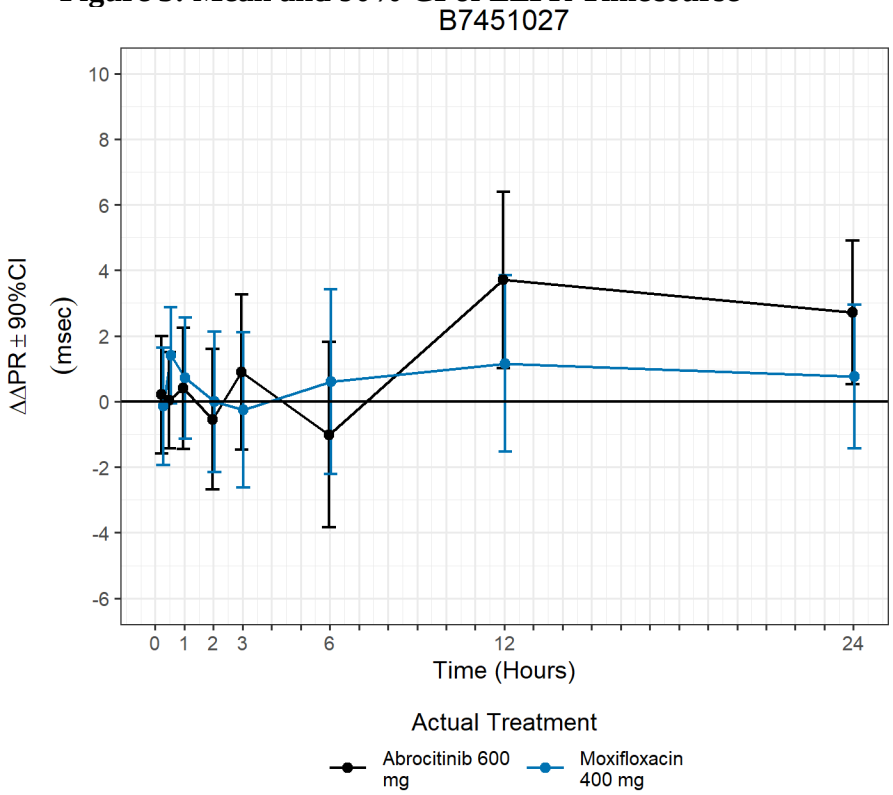
Figure 2: Mean and 90% CI of ΔΔHR Timecourse



4.3.3 PR

Figure 3 displays the time profile of ΔΔPR for different treatment groups.

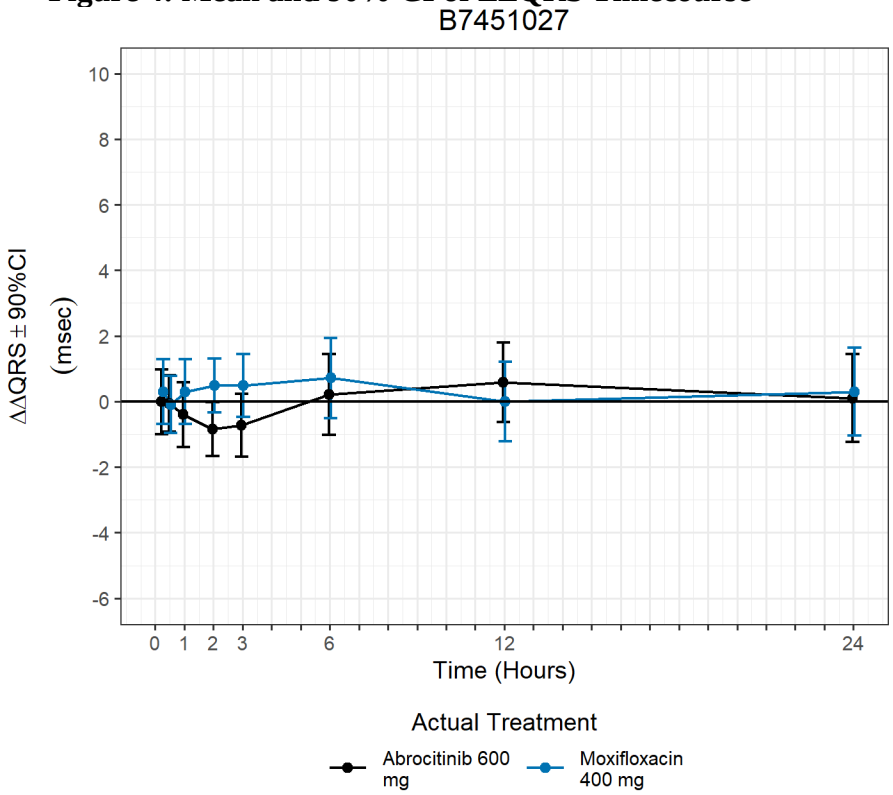
Figure 3: Mean and 90% CI of ΔΔPR Timecourse



4.3.4 QRS

Figure 4 displays the time profile of ΔΔQRS for different treatment groups.

Figure 4: Mean and 90% CI of ΔΔQRS Timecourse



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements either using absolute values, change from baseline or a combination of both. The analysis was conducted using the safety population and includes both scheduled and unscheduled ECGs.

4.4.1 QTc

None of the subjects experienced QTcF greater than 480 msec and ΔQTcF greater than 30 msec in Abrocitinib 600 mg dose group.

4.4.2 HR

None of the subjects experienced HR greater than 100 beats/min in Abrocitinib 600 mg dose group.

4.4.3 PR

None of the subjects experienced PR greater than 220 msec in Abrocitinib 600 mg dose group.

4.4.4 QRS

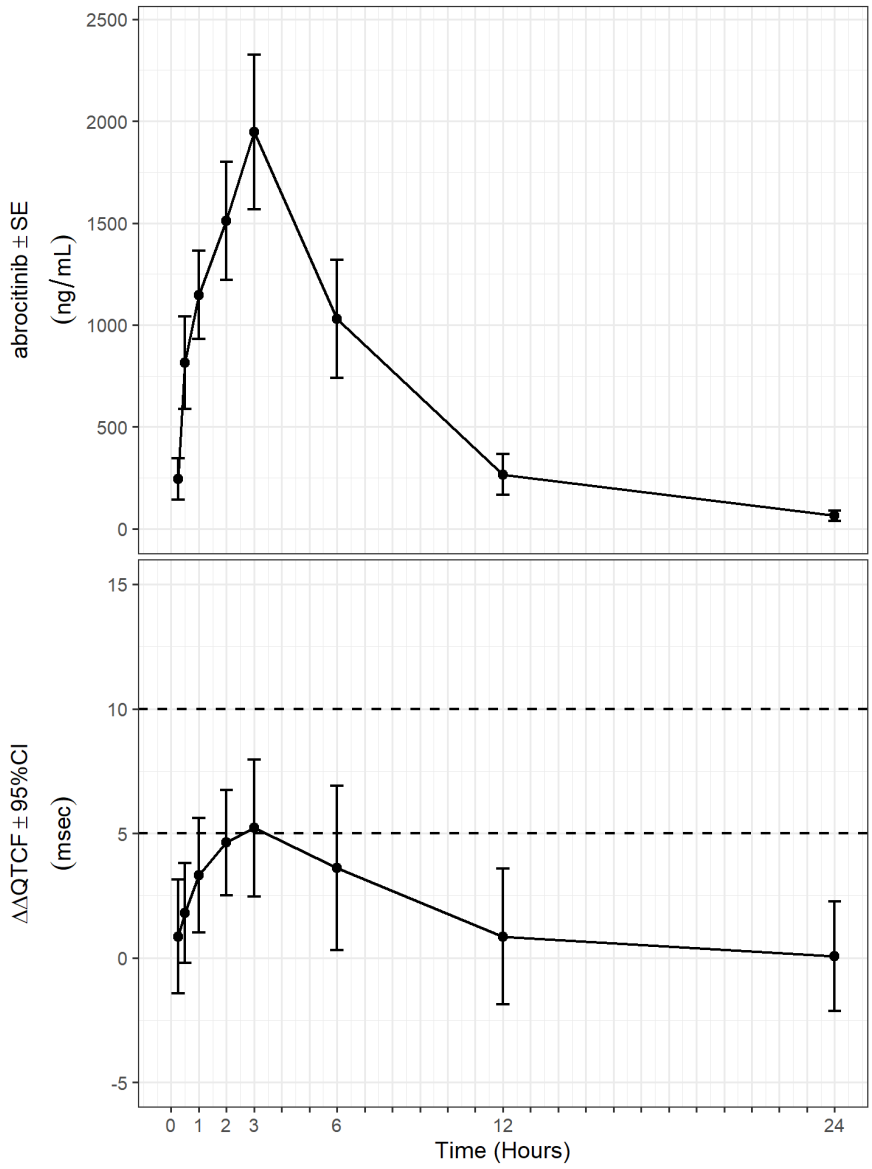
None of the subjects experienced QRS greater than 120 msec in Abrocitinib 600 mg dose group.

4.5 EXPOSURE-RESPONSE ANALYSIS

The objective of the clinical pharmacology analysis was to assess the relationship between plasma concentration of abrocitinib and ΔQTcF. Exposure response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG with time-matched PK.

Prior to evaluating the relationship between abrocitinib concentration and QTc using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between abrocitinib concentration and ΔQTc and 3) presence of non-linear relationship.

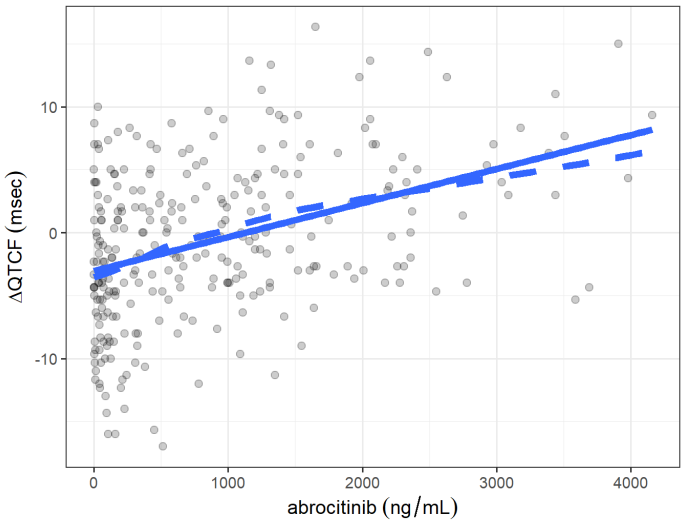
Figure 5: Time course of drug concentration (top) and QTc (bottom)



An evaluation of the time-course of abrocitinib concentration and changes in ΔΔQTcF is shown in Figure 5. There was no apparent correlation between the time at maximum effect on ΔQTcF and peak concentrations of abrocitinib indicating no significant hysteresis. Figure 2 shows the time-course of ΔΔHR, which shows an absence of significant ΔΔHR changes and the maximum change in heart rate is below 10 bpm (Sections 4.3.2 and 4.4.2).

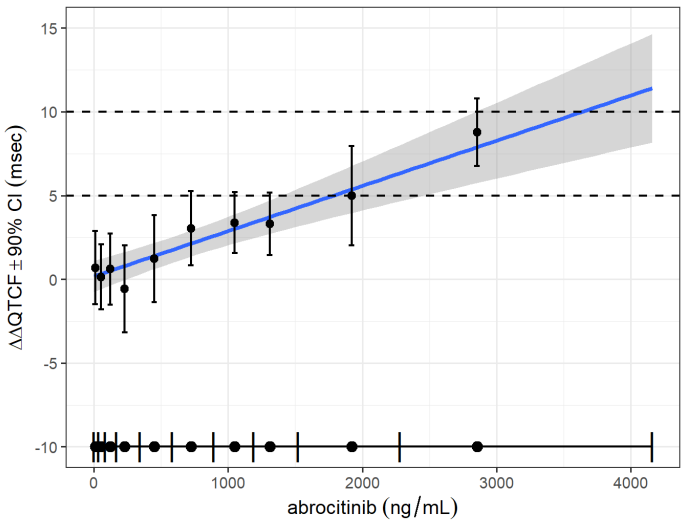
After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between abrocitinib concentration and ΔQTcF was evaluated to determine if a linear model would be appropriate. Figure 6 shows the relationship between abrocitinib concentration and ΔQTc and supports the use of a linear model.

Figure 6: Assessment of linearity of abrocitinib concentration-QTc relationship



Finally, the linear model was applied to the data and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTc model are provide in Table 1.

Figure 7: Goodness-of-fit plot for QTc



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DEVI KOZELI on behalf of MICHAEL Y LI
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Signing on behalf of Mike as he is on leave

CHRISTINE E GARNETT
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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	December 2, 2020
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 213871
Product Name, Dosage Form, and Strength:	abrocitinib tablet, 50 mg, 100 mg, 200 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Pfizer Inc.
FDA Received Date:	August 25, 2020
OSE RCM #:	2020-1836
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 REASON FOR REVIEW

As part of the approval process for (abrocitinib) tablet, 50 mg, 100 mg, 200 mg, the Division of Dermatology and Dentistry (DDD) requested that we review the proposed labels and labeling for areas that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the Prescribing Information (PI), Medication Guide (MG), and container labels. We find the PI and MG acceptable from a medication error perspective. However, the container labels can be improved to prevent wrong strength/dose errors and to facilitate product identification. We note the use of the placeholder "TRADENAME" for the proprietary name. We recommend the placeholder, "TRADENAME" be removed throughout the labels and labeling once a new name is found conditionally acceptable.

4 CONCLUSION & RECOMMENDATIONS

We find the PI and MG acceptable from a medication error perspective. However, the container labels can be improved prevent wrong strength/dose errors and to facilitate product identification.

4.1 RECOMMENDATIONS FOR DIVISION OF DERMATOLOGY AND DENTISTRY (DDD)

A. General Comments

1. We recommend the placeholder, “TRADENAME” be removed throughout the labels and labeling once a new name is found conditionally acceptable.

4.2 RECOMMENDATIONS FOR PFIZER INC.

We recommend the following be implemented prior to approval of this NDA:

A. Container Labels

1. Once a proprietary name is found conditionally acceptable, the placeholder “TRADENAME” must be replaced with the proprietary name on the container labels and the revised labels must be submitted to the Agency for review.
2. The similarity of the product code numbers has led to selecting and dispensing of the wrong strength and wrong drug. The middle digits are traditionally used by healthcare providers to check the correct product, strength, and formulation. Therefore, assignment of similar numbers for the middle digits is not an effective differentiating feature (e.g., -0235- for the 50 mg, -0335- for the 100 mg and -0435- for the 200 mg). Revise the product code in the NDC numbers to ensure that the middle 4 digits are not similar between the strengths. If for some reason that middle digits cannot be revised, increase the prominence of the middle digits by increasing their font size in comparison to the remaining digits in the NDC number or put them in bold type. For example: XXXX-**XXXX**-XX.
3. Consider adding “Do not crush, split, or chew the tablets.” in between the strength and net quantity. Additionally, from post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement. As an alternative, relocate the net quantity statement away from the product strength.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for abrocitinib received on August 25, 2020 from Pfizer Inc..

Table 2. Relevant Product Information for abrocitinib	
Initial Approval Date	N/A
Active Ingredient	abrocitinib
Indication	(b) (4)
Route of Administration	oral
Dosage Form	tablet
Strength	50 mg, 100 mg, 200 mg
Dose and Frequency	1 tablet orally once daily
How Supplied	film-coated tablets in 30 count bottles
Storage	Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C to 30°C (59°F to 86°F). Keep in original package
Container Closure	bottles

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following abrocitinib labels and labeling submitted by Pfizer Inc..

- Container Labels received on August 25, 2020
- Professional Sample Container Labels received on August 25, 2020
- Prescribing Information and Medication Guide (Images not shown) received on August 25, 2020, available from \\CDSESUB1\evsprod\nda213871\0002\m1\us\lab1423-lab1424-clean-pdf.pdf

G.2 Label and Labeling Images

Container Labels

(b) (4)

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

2 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

MADHURI R PATEL
12/02/2020 02:00:55 PM

SEVAN H KOLEJIAN
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